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ABNORMAL NITROGEN METABOLISM IN PATIENTS WITH THERMAL BURNS*

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THE burned patient is not a simple subject for metabolic study. In addition to the large amount of tissue breakdown and subsequent nutritional demands by the healing processes and the continuous loss of nitrogenous material from the burned surface, the burned patient is seldom free from intercurrent complications. Disturbance of renal or hepatic function may be present.[1] Local and sometimes general infections occur.[2] Shock may be an early complication and may have protracted secondary effects.[3] Fever may be present.[2] All these complications may cause severe disturbances in metabolism. In spite of these difficulties, a study of the nutritional requirements of the severely burned patient appears to be necessary since the healing of the burned surface may depend, in part, on the maintenance of good nutrition.

This paper presents certain observations on the disturbances of nitrogen metabolism in severely burned patients admitted to the Boston City Hospital as the result of the Cocoanut Grove disaster. In a subsequent report,[4] methods for controlling some of these abnormalities in nitrogen metabolism will be presented, and detailed observations on one severely burned patient are given elsewhere.[5]

AZOTEMIA

Azotemia is a known complication of the severely burned patient,[6] and two distinct types were occasionally observed in the present study.

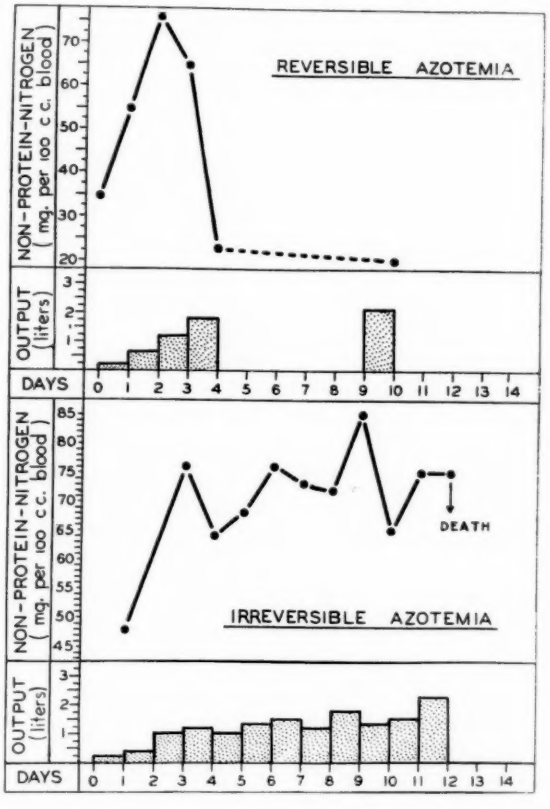

FIGURE 1. *Reversible and Irreversible Azotemia, associated with Early Oliguria, in a Severely Burned Patient.*

A reversible azotemia, associated with transitory oliguria, occurred frequently as an early complication. A typical example of this type of increase in the nonprotein nitrogen of the blood is shown in the upper part of Figure 1. This phenomenon is similar to that frequently found following surgical operations and in shock, when oliguria,

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or even anuria, may persist for some hours. In this type of azotemia, the restoration of a normal urine output results in a return of the increased nonprotein nitrogen level of the blood to normal. Since, however, the kidney can clear urea only at a fairly fixed maximum rate, the azotemia may persist for several days, as is shown in the patient illustrated in the figure.

Another type of azotemia was found in certain burned patients studied because of the presence of hemoglobinemia and hemoglobinuria. These problems will be discussed elsewhere.[7] This type of azotemia occurred only in severely burned patients. In these patients from 20 to 55 per cent of the body was burned, and much of the burn was third degree. With one exception, they secreted an acid urine. In a group of 9 patients having these criteria, 6 showed azotemia. In 5 of them the azotemia was irreversible, and in 1 it was reversible.

The nonprotein nitrogen in irreversible azotemia did not rise to the high values usually encountered in renal shutdown and complete anuria. The level was quite constant and seldom rose above 80 to 100 mg. per 100 cc. of blood. A typical example of irreversible azotemia in one of the patients studied is shown in the lower half of Figure 1. It will be noticed that oliguria was present early but that a normal urine output was soon obtained. The urine did not have a fixed specific gravity. In spite of this, the nonprotein nitrogen of the blood did not fall. The patient died on the twelfth day following her injury. It is of some practical importance that sulfadiazine administered to patients with irreversible azotemia gave satisfactory blood levels of the drug and was apparently well cleared by the kidney. Under no circumstances was the drug administered until a normal diuresis was obtained.

It is known that the excretion of hemoglobin in an acid urine may result in deposition of hemoglobin or its derivatives in the kidney.[7, 8] If, however, this was the primary cause of the azotemia, the damage to the kidney was not complete, since, except for an early transitory oliguria, the urine output was normal in volume and total solids. It is therefore suggested that in patients such as have been described an irreversible azotemia can occur owing to a partially damaged kidney. It is also probable that the increased rate of protein catabolism in such severely burned patients was an important additional factor in the production of a high nonprotein nitrogen in the blood. The damage to the kidney alone was not of sufficient severity to account for the nitrogen retention.[7]

Nitrogen Partitions of Blood and Urine

A partition of the nitrogenous constituents of the blood and urine of 3 patients with severe burns was done. The data of one patient are given in Tables 1 and 2. This patient sustained a thermal burn involving 45 per cent of her body, with 30 per cent third-degree and 15 per cent second-degree burns. She had hemoglobinemia and hemoglobinuria as early complications.

Table 1. *Partition of the Nitrogen in the Blood of a Severely Burned Patient.*

Day	Non-protein Nitrogen	Urea Nitrogen	Creatinine Nitrogen	Creatine Nitrogen	Amino Acid Nitrogen	Residual Nitrogen
	mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*
5	75.6	53.2	1.5	0.7	4.4	15.8
6	72.8	53.7	1.6	0.5	4.0	13.1
7	71.1	54.4	1.5	2.0	4.6	8.5
8	85.6	53.2	1.3	2.2	4.6	24.2
9	65.0	45.3	1.0	0.7	4.1	13.8
10	75.0	49.3	1.0	1.8	4.7	18.2
11	74.9	51.1	0.9	1.6	4.6	16.7

Irreversible azotemia was present, and as shown in Table 1, a portion of the elevated nonprotein nitrogen was accounted for by an increased urea. However, there was present in the blood a relatively large amount of residual or undetermined nitrogen. This residual nitrogen is probably that referred to by Duval et al.[9] and Lambret et al.[10] as "polypeptide nitrogen." The characterization of this fraction by these authors, however, is far from conclusive.

As shown in Table 2, there was also an increase in the residual nitrogen of the urine. This high level could be equally well accounted for by the excretion of abnormal metabolites or by the presence in the urine of substances that interfered with the action of urease.

Characterization of the residual nitrogen was not attempted. On hydrolysis, it yielded both amino and amido nitrogen. In the present study, the occurrence of a high blood residual nitrogen was not uncommon in severely burned patients, but high urine residual nitrogen was quite rare.

The azotemia illustrated in Table 1 can be accounted for on the basis, previously stated, of the production of large amounts of protein degradation products in the presence of a partially damaged kidney. Liver disease cannot, however, be ruled out in the present series of cases, in spite of the fact that there was no clinical evidence of its presence in the patients studied.

Hypoproteinemia

The presence of hypoproteinemia in burned patients has previously been commented on.[2, 6] In the present survey, 81 patients with burns were

studied. In 40, hypoproteinemia developed. There appeared to be a definite correlation between the progressive type of hypoproteinemia and the severity of the burn. For example, in 12 patients having burns of between 10 and 50 per cent of the body surface, 8, or 65 per cent, showed progressive hypoproteinemia. In 51 cases with burns involving less than 10 per cent of the body surface, however, only 8, or 15 per cent, showed this abnormality. Early hypoproteinemia was probably associated with protein loss from the burned areas, but other causes must be looked for to explain the progressive type of hypoproteinemia occurring in severely burned patients. This hypoproteinemia increased in severity until the anasarca level was reached and massive edema developed.

The fall in albumin and the reversal of the albumin-globulin ratio encountered early may be theoretically associated with the preferential loss of albumin from the circulating blood owing to the relatively low molecular weight of albumin as compared with that of globulin. It has been noted, as shown in Figure 2, that the albumin level may remain constant while the globulin fraction actually rises in the circulating blood. Such rises in the globulin have frequently been associated with infection and with hepatic dysfunction, as judged by clinical and laboratory evidence. In a few cases, however, postmortem examination showed some degenerative changes. This subject will be reported on by others.[11]

It appears necessary to seek causes other than early plasma loss to explain the hypoproteinemia of burns. It is a frequent observation that burned patients remaining in a hospital for long periods of time while awaiting skin grafting lose considerable amounts of weight. An opportunity has been given us to study such patients. We found that severely burned patients rapidly lost large amounts of nitrogen into the urine. As shown in Table 3, the nitrogen loss on occasion amounted to as much as 45 gm. a day. It is well known that the excretion of abnormally large amounts of nitrogen occurs in thyrotoxicosis, in severe infections and in other conditions associated with increased metabolism, and it has also been reported as occurring in burned patients.[6] It has been thought to be due to a rapid destruction of structural protein and has been called by some authors "toxic protein destruction." Obviously, such losses of nitrogen into the urine may cause a marked protein deprivation.

In all burned patients admitted to this hospital, an attempt was made to meet the demand for protein by increasing the protein intake to from 100 to 125 gm. a day. Even at this level, there was a marked negative nitrogen balance in 9 patients with severe burns. Most of the patients with minor burns of less than 10 per cent of the body surface involved responded to the intake of 125 gm. of protein a day with a return of their plasma protein to normal, but in those patients with a continued marked loss of nitrogen into the urine this did not occur. Indeed, in some of the severely burned patients, it has been calculated that, on the basis of the loss of nitrogen into the urine alone, 300 gm. of protein a day would have been required to maintain nitrogen equilibrium. In addition to this loss, some patients continued to lose large amounts of nitrogenous material from the burned surface for long periods of time. This insensible loss could not be calculated. The restoration of protein under these combined circumstances was a difficult problem, since the amounts required were con-

TABLE 2. *Partition of the Nitrogen in the Urine of a Severely Burned Patient.*

DAY	VOLUME	TOTAL NITROGEN	UREA NITROGEN	CREATININE NITROGEN	CREATINE NITROGEN	AMINO ACID NITROGEN	AMMONIA NITROGEN	URIC ACID NITROGEN	PROTEIN NITROGEN	RESIDUAL NITROGEN
	cc.	*gm./24 hr.*	*% total*	*% total*	*% total*	*% total*	*% total*	*% total*	*% total*	*% total*
5	1520	8.0	43.5	5.5	0.4	0.9	0.8	1.1	9.6	37.8
6	1600	8.4	20.6	5.2	0.2	1.1	0.4	1.2	1.0	70.2
7	1140	7.0	7.6	4.9	0.0	1.2	0.7	1.3	0.0	84.4
8	1800	12.9	28.7	3.7	1 1	0.9	–	0.9	7.7	57.1
9	1490	11.2	10.0	3.0	0.3	0.9	1.6	0.6	6.3	77.2
10	1580	11.4	13.4	3.3	2.4	0.8	1.7	1.0	1.8	75.7
11	1970	13.9	5.0	3.0	2.7	1.0	2.1	0.6	2.9	82.7

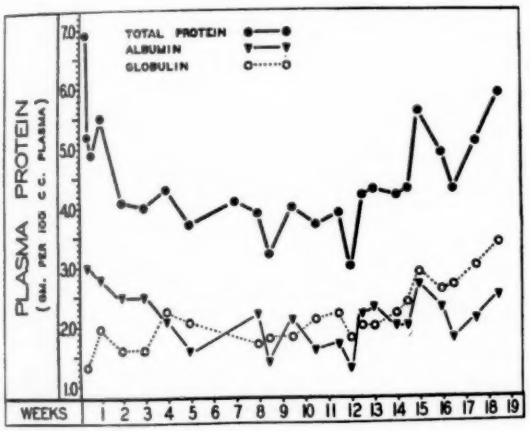

FIGURE 2. *Plasma Protein Fractionation Showing Early and Late Reversal of the Albumin-Globulin Ratio.*

siderably greater than those the patients could ingest.

A loss of as much as 30 per cent of the body weight has occurred, in some of the patients studied, as a result of failure to maintain adequate nutrition. Therefore, in severely burned patients, a careful appraisal of the nitrogen balance must be made early, and when marked deficits of nitrogen are expected, forced alimentation by a variety of routes should be begun. The problem becomes increasingly difficult as time goes on, so that whatever measures are to be used to ameliorate the nutritional deficits must be commenced early. It must also be remembered that estimation of the nitrogen requirements of a burned patient by the usual nitrogen balance studies alone give only the minimum requirement. For example, as shown in Figure 3, in one patient, after positive nitrogen balance was restored by gastric intubation and intravenous amino acid, over 8000 gm. of protein was laid down in a period of six weeks without unusual increases in urine nitrogen and with evidence of complete utilization. Even after this apparently large nitrogen retention was established, the patient was still fifty pounds below the admission weight.[5]

TABLE 3. *Excessive Total Nitrogen Excretion, Expressed in Grams per 24 Hours, in Severely Burned Patients.*

Hosp. No.	Day																	
	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1088906	6	17	9	32	9	10	7	13	9	10	11	7	4	8	9	10	8	9
1088895	–	21	22	9	21	25	17	18	19	45	19	33	28	21	38	9	10	13
1088910	13	16	18	17	–	26	23	14	15	12	11	2	14	15	4	24	21	16
1088930	10	20	21	–	15	11	25	5	8	14	10	10	11	11	12	11	11	5
1088865	–	–	22	–	5	13	14	9	11	12	14	8	–	3	16	10	8	15
1089011	–	11	18	10	15	17	19	22	19	19	28	16	–	14	17	16	14	14
1088976	–	22	33	9	17	16	29	11	14	13	17	21	8	9	–	4	16	11
1088892	19	–	34	23	24	30	26	9	30	11	11	24	26	20	19	14	13	20
1089013	–	17	9	12	17	8	14	18	13	14	18	17	19	20	25	24	22	19

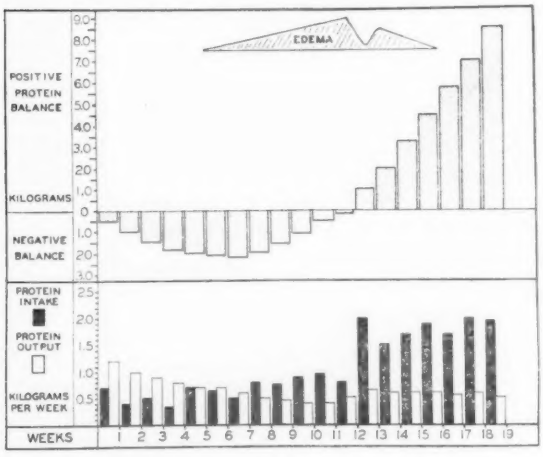

FIGURE 3. *Nitrogen Balance in a Severely Burned Patient.*

Practical considerations of how this problem may be attacked from a nutritional standpoint will be presented in a subsequent communication.[4]

SUMMARY AND CONCLUSIONS

In a series of burned patients, azotemia was a common complication of severe burns and was usually of the reversible type. It occurred early and was relieved when the urine output became normal. In some severely burned patients, an irreversible type of azotemia occurred. This increase in nonprotein nitrogen was not progressive and may have been due to a partially damaged kidney in the presence of increased protein catabolism. So far this type of azotemia has been chiefly found in severely burned patients excreting an acid urine in whom hemoglobinemia and hemoglobinuria were present.

In certain severely burned patients having coincidentally hemoglobinemia and hemoglobinuria, there was an abnormality in the partition of both the blood and the urine nitrogen, associated with the presence of large amounts of residual or undetermined nitrogen. The percentage of total nitrogen of the urine present as urea was low.

Hypoproteinemia was a common finding in the severely burned patients. A transitory hypoproteinemia was associated with plasma loss and could be restored by simple dietary means, but the more progressive type was probably due to the loss of large amounts of nitrogen into the urine owing to increased protein catabolism, in addition to large losses of nitrogenous material at the burned surface.

Inversion of the albumin and globulin ratio frequently occurred. When it happened early, it was probably associated with a preferential loss of albumin, which has a low molecular weight. The cause of its late occurrence in burned patients has not been determined.

The serious problem of the maintenance of adequate nitrogen metabolism in severely burned patients is briefly outlined.

References

1. Wilson, W. C., Macgregor, A. R., and Stewart, C. P. Clinical course and pathology of burns and scalds under modern methods of treatment. *Brit. J. Surg.* **25**:826-865, 1938.
2. Harkins, H. N. *Treatment of Burns.* 457 pp. Springfield, Illinois: Charles C Thomas, 1942. Pp. 135-151.
3. Blalock, A. Experimental shock: importance of local loss of fluid in production of low blood pressure after burns. *Arch. Surg.* **22**:610-616, 1931.
4. Levenson, S. M., Davidson, C. S., and Taylor, F. H. L. Unpublished data.
5. Taylor, F. H. L., Levenson, S. M., Davidson, C. S., Browder, N. C., and Lund, C. C. Problems of protein nutrition in burned patients. *Ann. Surg.* **118**:215-224, 1943.
6. Lucido, J. Metabolic and blood chemical changes in severe burn: case report. *Ann. Surg.* **111**:640-644, 1940.
7. Shen, S. C., Ham, T. H., and Fleming, E. M. Studies on destruction of red blood cells. III. Mechanism and complications of hemoglobinuria in patients with thermal burns: spherocytosis and increased osmotic fragility of red blood cells. *New Eng. J. Med.* **229**:701-713, 1943.
8. DeGowin, E. L., Warner, E. D., and Randall, W. L. Renal insufficiency from blood transfusions. II. Anatomic changes in man compared with those in dogs with experimental hemoglobinuria. *Arch. Int. Med.* **61**:609-630, 1938.
9. Duval, P., Roux, J.-Ch., and Goiffon. Essai sur l'intoxication par les polypeptides. *Presse méd* **42**:1785-1787, 1934.
10. Lambret, O., Driessens, J., and Warembourg, H. Le syndrome humoral des brûlures. *Compt. rend. Soc. de biol.* **123**:10, 1936.
11. Leary, T. Personal communication.

PREVENTION OF VITAMIN DEFICIENCIES IN WARTIME*

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THE prevention of vitamin deficiencies is an important problem and, if the duration of the war is prolonged, a serious one. Unquestionably, nutritional deficiencies already exist in the occupied countries, and the United States will have to play a large part in the feeding of those peoples at a later date. We are shipping an ever-increasing amount of food to the United Nations and to our troops abroad.

Our government has instituted a program with which we are all familiar. This includes rationing foodstuffs, increasing production on the farm and in Victory gardens, and preserving food in the home to conserve manpower and material. The Council on Foods and Nutrition of the American Medical Association and the Food and Nutrition Board of the National Research Council function jointly to advise on the rationing of food and the institution of educational programs relative to the food problem.

Vitamin deficiency is but one phase of nutrition. It happens to be the newest one, and the one in which a tremendous amount of work has been done in an incredibly short time. The therapeutic use of vitamins has become routine in all branches of medicine. The altered physiologic states associated with specific vitamin deficiencies are, in general, well recognized and well treated. There are also the milder, less well-recognized, multiple deficiencies that are usually the province of the internist or the general practitioner.

The public mind is readily captivated by the concept of vitamins and their alphabetical nomenclature. Health-giving properties and the vitamin content of processed foods are emphasized. Newspaper and radio advertising has aroused public consciousness. Over-the-counter sales of attractively colored and packaged vitamin preparations have reached tremendous proportions.

Obviously, the answer to the prevention of deficiencies in the face of increasing food shortage in the future is not more and bigger vitamin pills. This is not so facetious as it might sound, and the physician may have contributed at times to the impression that vitamins by definition are found in pills. To prescribe such preparations without having inquired into the patient's diet and without making obvious corrections is but a gesture in the right direction. There is not sufficient material to supplement the diet of the entire population by concentrates and synthetic material, even if it were economically possible to do so. With rationing and such shortages as already exist, many items that are the richest sources of vitamins are unobtainable in sufficient amounts to be included in the daily diet. It becomes necessary to look a little farther down the list, so to speak, and include larger amounts of less rich but more available foods.

This is well illustrated by ascorbic acid. People have largely depended on a daily intake of orange, pineapple or tomato juice — now obtainable only in limited quantity. The logical answer is the increased consumption of cabbage as salad or of potatoes properly cooked. All fruits, berries and vegetables contain significant amounts of ascorbic acid. In England a Walt Disney-like character called "Johnny Potato" is used in cartoons and posters to popularize the increased consumption of potatoes. Approved methods of cooking are published and prizes offered for novel ways of preparing potatoes without destroying their ascorbic acid content.

Many publications contain tables giving the vitamin values of particular food sources. These are usually unreliable and misleading. They are often based on the fresh, uncooked animal or

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 26, 1943.

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vegetable source. The ascorbic acid content of green vegetables and fruits, for example, increases steadily to a maximum just before the fruit is ripe and then decreases steadily. The amount in a given fruit or vegetable is also influenced by proper fertilization and methods of growing. With many fruits an added factor is whether they are tree ripened or picked while green and allowed to ripen in storage. Further, the amount of vitamins contained in food after cooking or preservation varies as the process involves cooking, heating, washing, bleaching or the addition of chemicals. It can be readily appreciated that this multiplicity of factors makes for a wide difference in specimens of food as they are found on the table.

There has been set up a table of figures by the Council on Foods and Nutrition of the American Medical Association giving what constitutes daily vitamin requirements in the light of present-day knowledge. These are admittedly an approximation and at best a rough estimate. Changes must be made relative to age, pregnancy, lactation, infection and specific diseases. Revision of these figures tends to be upward as knowledge concerning the requirements is accumulated. It is well to have some basic table in mind as a point of departure. Special requirements with reference to altered physiologic states and specific diseases will not be discussed, as the present rationing system permits additional food in such cases at the request of the physician.

All known vitamins with the exception of vitamin D are synthesized by plants and used by them essentially for the same purpose as by man and animals. Man, however, is unable to synthesize these compounds, with the exception of vitamin D, and must depend on ingestion for his supply of vitamins or their precursors. Vitamins do not furnish energy and are not building units for the structure of the body, but are necessary for the transformation of energy and the regulation of metabolism. There are many gaps in the details of the physiological chemistry of these substances, but evidence has accumulated so far as the better-known vitamins are concerned regarding the general role that they play in the body. There is also a long list of lesser-known substances that apparently contain vitamins. The knowledge of these is fragmentary, their role in the human body is unknown, and no estimate concerning their requirements can be formed. These will not be discussed, but a review of the better-known vitamins should serve to indicate under present conditions the principal available sources, the changes in diet and certain points of preparation of food in order to prevent avitaminosis.

There is not much danger of avitaminosis so far as the A group of vitamins is concerned, provided that there is an adequate intake of vegetables. The daily requirement for the average person is 5000 international units. This is not increased during body activity, but is greater in lactation and pregnancy. Excluding restricted and scarce items, such as dairy products, eggs and liver, the principal sources are green-leafy and yellow vegetables. A single serving — that is, 3½ to 4 ounces of beet tops, kale, mustard greens, spinach or turnip greens — will supply well over twice the daily requirement. A serving of carrots will supply about the same amount. The same serving of summer squash will provide a little over the daily requirement, and sweet potatoes a little under it.

As another approach to prevention of vitamin deficiency in the A group, the Council on Foods and Nutrition has recommended the fortification of oleomargarine to a level of 9000 international units per pound, so that 1 ounce will provide one fifth the daily allowance. The fortification and wider sale of oleomargarine is barred by law in some states and is opposed by dairymen, but there is no question that it provides a suitable vehicle for vitamin A. There is little difference between butter and oleomargarine except for a lower percentage of unsaturated fatty acids in the latter.

In considering the prevention of deficiencies in the vitamin B group, it should be pointed out that the deficiency of a single factor is an exception rather than the rule. These vitamins resemble enzymes and are concerned with the utilization of specific food substances. For example, the riboflavin enzyme system is concerned with the utilization of the essential amino acids, and a deficiency of such amino acids would eventually produce the clinical picture of riboflavin deficiency.

The known members of this group consist of thiamine, riboflavin and niacin. The other members have not been identified or have been studied so inadequately that their function and requirements are unknown.

Thiamine is said to be required in a daily dose of 1.8 mg. for the average person. This requirement is increased with activity, and also during pregnancy and lactation. The outstanding source of thiamine is lean pork. One 4-ounce serving provides almost the daily requirement. The next richest source is dried brewer's yeast, an ounce of which is equal to about the same amount. Thiamine is usually obtained in small quantities from a great many foods, including meat and vegetables. The most available sources are whole-wheat bread and whole-grain cereals. Dried peas and beans are also important. The problem of thia-

mine deficiency is obviously more acute now, with the rationing of meat and a probable decrease in the supply of pork as the war continues. Furthermore, the available amount of brewer's yeast, which is the principal source of natural thiamine concentrates used therapeutically, is inadequate.

This problem was a real one in England and was solved satisfactorily by the increased consumption of peas, beans and other sprouts. The bread in current use for the last several years in England has been made from an 85 per cent extraction flour. Sydenstricker,* who recently described his experience in examining several thousand persons in all parts of the British Isles, stated that the incidence of vitamin B group deficiencies is extremely low. He added that many people were homeless and so closely touched by the war that their incentive to consume these rather unpalatable foods as a constant diet is greater than before.

It is of interest in this connection that one of the largest baking companies in the United States bought the Earle flotation process — a method of getting rid of the woody portion of the hull, which lends a bitter taste to cereal products. This company developed the process, adapted mills to its use, and attempted to market an almost 100 per cent whole-grain bread that was priced the same as the usual white loaf. In spite of a vigorous advertising campaign, the bread did not sell, although it was recommended by nutrition authorities. The experiment was given up except in a few communities that are used as a barometer for public buying tastes.

From a scientific standpoint it would seem that to extract and bleach flour, reducing the vitamin content to about 10 per cent of the whole grain and then fortify it with vitamin concentrates, is a wasteful procedure. On the other hand, if the public will not eat whole-grain bread, this may be the only way that a deficiency can be prevented. Bread also provides a useful vehicle for the addition of riboflavin to the diet.

The next most important factor in the vitamin B group is riboflavin. The requirement is approximately 2.7 mg. per day, or almost twice that of thiamine. The requirement is increased with activity, is in proportion to body weight, and is higher in lactation and pregnancy. Milk is the most important source; one pint supplies half the daily allowance. Meat is another important source, the usual serving supplying about one twelfth the daily allowance. The richest source is liver — 4 ounces yields over 3 mg. Riboflavin is readily destroyed by light; it is soluble in water and therefore there are losses in cooking. Omitting liver and brewer's yeast, which cannot be advocated for general use because of their limited supply, one comes again to the dried sprouts and vegetables such as peas, beans, spinach, cauliflower and peanuts. An increased consumption of these items, together with a pint of milk daily and the use of enriched bread, is the principal method of combating riboflavin deficiency. It should be emphasized that evaporated, powdered or skim milk can be substituted for fresh milk. It is important too that milk that stands in clear glass bottles in sunlight soon loses its riboflavin content.

Niacin, formerly called nicotinic acid, is the third important member of the vitamin B group. The daily allowance is ten times that of thiamine, or 18 mg. The outstanding source is liver, a 4-ounce portion containing somewhat more than the daily requirement. A serving of red meat will furnish from 7 to 10 mg. in each 4 ounces. Dried brewer's yeast in the amount of 1 ounce yields well over half the daily requirement. This vitamin is relatively stable to heat and there is little loss through cooking, although it is soluble in water. Here again, bran and whole-grain cereals are the most important available sources, although peanuts, potatoes and carrots must be included.

The members of the vitamin B group are often discussed together. Their high value in liver, brewer's yeast and meat, all of which are limited in supply, added to the fact that their best secondary source is whole-grain cereals and legumes, indicates a number of points in common. As already stated, there is reason to believe that the general public does not react favorably to dark whole-grain breads and cereals. Bakers are now launched on a program of enriching bread with these three factors. This may be the answer to the problem, although as the war continues it may prove necessary to return to peas, beans, dark bread and potatoes in far greater quantities than anyone would enjoy. The physician in his daily contact can do a great deal to encourage the use of these items. In order to increase the consumption of such carbohydrates fat is necessary: first, because carbohydrate is eaten more easily if it is greased with butter, margarine or drippings; and second, because fat acts as a thiamine sparer in the body.

It is of interest that tests have been conducted on bread to show the loss of vitamin in baking. The bottom crust may show a loss up to 34 per cent of the total thiamine, whereas the top crust may show a loss up to 13 per cent. Toasting a slice of bread destroys somewhere between 11 and 25 per cent of the total thiamine content, depending on the time of toasting and the thickness of the slice.

*Sydenstricker, V. P. An address given at the Medical College of Virginia, March, 1943.

A consideration of vitamin C shows little reason why there should be any extensive deficiency. Although transportation and preserving facilities limit the supply of the favorite sources, such as oranges, tomatoes and pineapple juice, an adequate intake of a variety of home-grown and preserved berries, fruits and vegetables will ensure sufficient vitamin C. Raw cabbage and potatoes are good sources. The average adult requires about 75 mg. The vitamin may be lost in cooking, both because it is soluble in water and because it is destroyed by oxidation.

Previous reference was made to the method of preparing potatoes. A 5-ounce serving of boiled or baked potato provides 25 mg. or about one third the daily requirement. When potatoes are fried, the ascorbic acid is cut in half. Mashed potatoes show a severe reduction in the vitamin C content, and whipped potatoes lose the entire amount.

Vitamin C has been shown to be present in sweat, as is thiamine. It is known that riboflavin is needed in proportion to body activity. It has been suggested that in addition to feeding salt tablets to defense workers in heavy industry or under conditions of increased heat, thiamine, riboflavin and ascorbic acid be added either in the form of concentrates or as further allowance of food.

The average adult has little possibility of developing a vitamin D deficiency except in conditions of unusually scant exposure to sunlight. This vitamin is synthesized by the body and there is excellent storage. In the winter months an adequate intake should be assured through the diet or by the routine ingestion of concentrates. The outstanding source is fish-liver oil. Some varieties contain as much as 40,000 international units per gram of extracted material. Others contain little or no vitamin D. Eggs are an excellent source, and liver is of definite value. The acuteness of the problem varies with the available supply of these items.

It has been demonstrated that irradiation gives cereals, meat, milk, eggs and various oils antirachitic properties. At the present time milk is the most suitable medium for irradiation and is available in most urban communities.

A point that is insufficiently emphasized with reference to the fat-soluble vitamins A and D is the ingestion of mineral oil. This substance is inert and is not absorbed. It has been conclusively shown that absorption of the fat-soluble vitamins does not take place to any extent from a mineral oil solution. There are many patients who use large amounts of mineral oil over long periods of time. The use of mineral oil salad dressing in reduction diets means the constant ingestion of mineral oil with the food and is of questionable advisability. If used, mineral oil is best taken at bedtime after digestion of the evening meal is completed, when it interferes as little as possible with the absorption of vitamins A and D.

Conclusions

Deficiency in the A group of vitamins can be avoided by the daily intake of green-leafy and yellow vegetables, and by the use of fortified oleomargarine when dairy products are unavailable in adequate amount.

Deficiency in the vitamin B group is best controlled by the use of fortified bread, and the physician should encourage the use of whole-grain bread and cereals. The constant use of toasted bread should be discouraged. The average adult should drink a pint of milk a day or its equivalent in the form of evaporated or dried milk used in food.

Ascorbic acid deficiency can be prevented by the increased use of a varied diet containing fruits, berries and vegetables.

Deficiency in the vitamin D group can best be prevented by adequate exposure to sunlight and the ingestion of eggs and liver when available. If these foods are unavailable, irradiation of food may become more widespread. The routine use of fish-oil concentrates may be advisable under special conditions.

The physician should assume greater responsibility in advising patients with regard to diet. The war may serve the purpose of improving food habits and introduce improved methods of cooking and preserving food.

1801 Beacon Street

ERYTHROBLASTOSIS FETALIS OF THE ICTERUS GRAVIS TYPE

Report of Two Cases With Recovery

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SALEM, MASSACHUSETTS

RECENTLY 2 babies showing erythroblastosis fetalis of the icterus gravis type were delivered at the Salem Hospital, and both recovered following a course of treatment instituted in accordance with the recently devised ideas concerning the etiology of this disease. These results seem of sufficient interest to warrant presentation of the cases.

The concept that the production of erythroblastosis fetalis is the result of isoimmunization of the mother to the Rh factor of the fetal erythrocyte, as first shown by Levine, Katzin and Burnham[1] following the demonstration of the existence of the Rh agglutinogen by Landsteiner and Wiener,[2] is now generally accepted, and both these cases fit into this already familiar pattern (Table 1). In accordance with this theory, therefore, the

TABLE 1. *Presence of Rh Agglutinogens in the Families Studied.*

CASE NO.	FATHER	MOTHER	SIBLING 1	SIBLING 2	SIBLING 3
1	+	—	+*		
2	+	—	+	+	+*

*Cases under discussion.

treatment of the newborn infant manifesting any one of the three clinical types of this syndrome should be directed toward maintaining a satisfactory level of hemoglobin and red cells within the circulation by the administration of Rh– blood of the proper group, so that the patient may be carried over the first crucial days by transfused blood until the anti-Rh substance within the circulation has been eliminated, the destruction of red cells by this phenomenon ended, and the immature cells allowed to mature normally and to assume the function of oxygen transport.

The mortality of erythroblastosis of the icterus gravis type has been generally accepted as relatively high, two publications giving the percentage as 80[3] and 75 per cent.[4] The recovery in the cases here presented, although perhaps not statistically significant, seems to be important and in accord with the changed concept of the fundamental physiology and indications for treatment of this disease. In retrospect, the results indicate that the previously accepted therapy in such cases, which usually consisted of administering blood taken from the father or some member of the family of the same blood group as the infant and compatible by the usual technic of cross-matching set up at room temperature, has oftener than not been deleterious. The probability is that these donors were of the Rh+ type and that administration of their blood to the infant added insult to injury by supplying the blood stream with more cells to be agglutinated by the anti-Rh substance in the circulation.

It seems worth while to point out, although it has been previously stressed in a recent paper and editorial in the *Journal*,[5, 6] that determination of the presence or absence of Rh agglutinogens in the blood of the donor should be done before transfusion of the infant showing evidence of erythroblastosis, or of the mother if indicated, and that this procedure ordinarily takes two hours according to the original technic of Landsteiner and Wiener.[2] With the use of human anti-Rh serum the test can be read in a shorter period of time, usually within an hour.

Although we agree entirely with the suggestion that Rh typing should be routine before all transfusions, it also seems important that it be commonly understood that the agglutinin operating in this phenomenon has a very narrow range of temperature specificity, operating at body temperature (37.5°C.) but not at ordinary room temperature. This lack of knowledge of the zone of temperature specificity provides an explanation of why seemingly properly grouped transfusions between the father or other persons and the infant, before the knowledge of the Rh factor was available, proved to be harmful. Therefore, it seems reasonable that anyone showing evidences of the result of isoimmunization to the Rh factor, whether it be the infant or the mother, and — equally important — any Rh– patient receiving multiple blood transfusions, should be safeguarded by setting up the crossmatching at a temperature of 37.5° C. for at least thirty minutes, or longer if possible. In small hospitals where Rh determinations with known anti-Rh serums are not routine because of several factors — including an insufficient number of typings to keep changing personnel familiar with the interpretation of the test,

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which is a difficult procedure, the expense and the fairly rapid deterioration of the typing serum—crossmatching at 37.5°C. is easily carried out, and its interpretation by inexperienced persons is simple. It not only detects Rh incompatibility, and must be done to supplement Rh typing, but

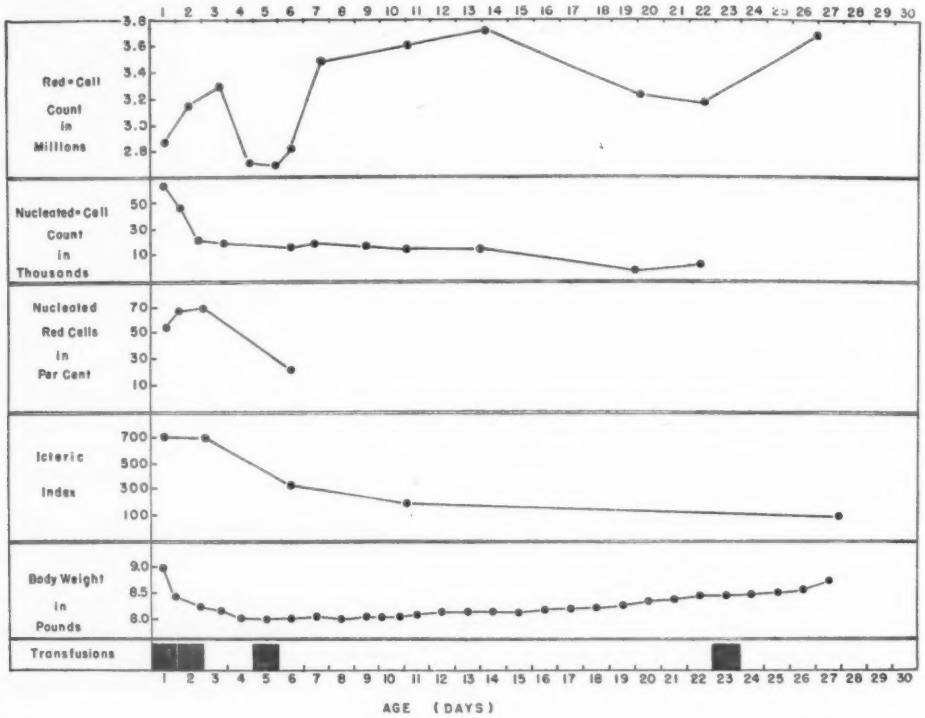

FIGURE 1. *Case 1.*

may also demonstrate agglutination due to blood subgroup incompatibilities, and furthermore can be done quickly in emergencies.

Another departure from the routine care in these 2 cases was to forbid nursing by the mother. This was done on the assumption that the anti-Rh substance might be transmitted through the breast milk, a possibility suggested by a recent case report.[7] Since both these children were critically ill, it was thought unwise to jeopardize them further by allowing them to nurse.

A problem that is unanswerable at the present time but is highly pertinent is whether in this type of erythroblastosis permanent damage to the brain may result from the severe degree of kern-icterus. This was probably present in each of these cases, since the icteric index at its peak was estimated at 600 and 700, respectively. All that can be said is that after four months there is no clinical evidence of damage to the central nervous system in either case.

CASE 1. F. I. H. This patient was the result of a second pregnancy, the first having resulted in a miscarriage suggesting Rh isoimmunization. Both parents were healthy, with no history of tuberculosis, diabetes or blood dyscrasias. The health of the mother during this pregnancy was uneventful.

The patient, an 8-pound, 15-ounce girl, was delivered normally after a 12-hour labor with Nembutal and scopolamine medication, supplemented during the second stage with nitrous oxide, oxygen and ether. Considerable meconium was passed during the delivery, and at birth the patient was covered with bright-yellow vernix caseosa. Because of this, and because the placenta was large and edematous, a specimen of the cord blood was sent to the laboratory to be examined for the Rh factor and was subsequently reported as positive. No anti-Rh substance could be demonstrated in the maternal blood 5 days after delivery.

Twelve hours after delivery, because of respiratory distress, a pediatric consultation was obtained. Physical examination at that time showed deep, golden-yellow jaundice of the skin and scleras, in addition to marked pallor and respiratory distress. The latter was thought to be due in part to the existing anemia as well as to a distended abdomen, caused mostly by a greatly enlarged liver that reached nearly to the iliac crest and by an enlarged spleen that was felt 3 fingerbreadths below the left costal margin. The kidneys were not palpable. The heart was not enlarged and its action was good, with no murmurs. The blood-cell count showed 2,880,000 erythrocytes, 58,000 nucleated cells, of which 51 per cent were red cells, and a hemoglobin of 12.6 gm. (Fig. 1).

Because of pallor and respiratory distress the patient was placed in an oxygen tent. A transfusion of 60 cc. of citrated Rh– blood was given at 12 hours of age, and was repeated at 36 hours because extensive edema of the skin, eyes, scalp, chest, legs and arms had developed.

Following the second transfusion, the patient was removed from the oxygen tent, since the generalized edema had begun to subside and the respirations and color had improved. The icteric index remained at 700. Urinalysis revealed a positive test for bile, a slight trace of albumin and some white and red cells in the sediment. There was no vomiting of the formula. The nutrition was good. The reflexes were not hyperactive, and development seemed to be progressing normally.

At thirteen months of age, this child had six erupted deciduous teeth, all of which had a deep greenish appearance, presumably due to discoloration by bile pigment;

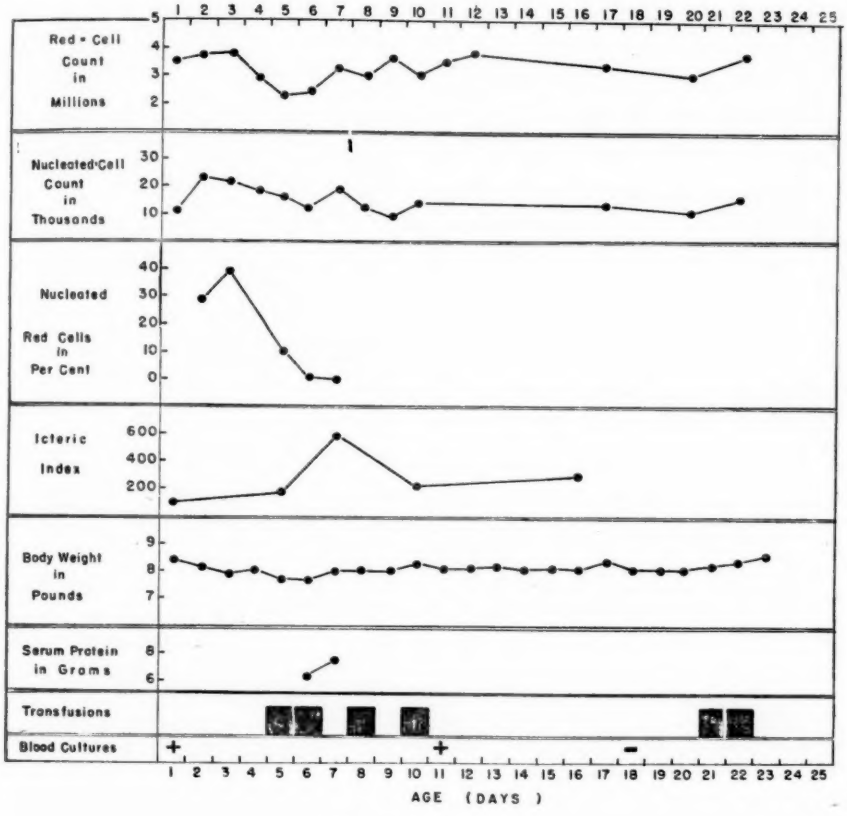

FIGURE 2. *Case 2.*

The nonprotein nitrogen was 91 mg. and 44 mg. per 100 cc. on successive examinations during convalescence. There was no albumin, bile or cells in the urine at discharge. The serum protein fell to 5.15 gm. per 100 cc. on the 5th day, and because the hemoglobin had dropped to its lowest value (11.6 gm.) and the red-cell count was 2,600,000, a third transfusion of 60 cc. of Rh− blood was given. The blood for all three transfusions was from the same donor. Just before discharge a fourth transfusion was given, using the same donor. The stools revealed negative guaiac tests and negative cultures for pathogenic organisms, and bile tests, at first positive, were negative at the time of discharge. A blood culture taken on the 4th day of life was reported positive for *Staphylococcus aureus*, with slight hemolysis. A repeat culture was not obtained because the external jugular veins were thrombosed, and on account of the later course, the organism was thought to have been a contaminant. A Hinton test on the cord blood was negative. The patient was not allowed to nurse and took well, with little vomiting, a modification of milk, water and Karo.

At discharge the skin still had a moderately jaundiced hue, but on subsequent check-up examination this had completely disappeared and the patient seemed well. this serves as confirmatory evidence of the marked jaundice at birth.

CASE 2. M. I. M. This patient was the third baby in the family, the two other siblings being a healthy boy and girl aged six and three years, respectively. There was no history of familial disease, including blood dyscrasias. The mother had no complications during this pregnancy and after a short labor was delivered normally of an 8½-pound boy.

At delivery several purplish spots were scattered on the baby's skin. The temperature was 96°F. rectally. He was jaundiced. Vitamin K was given intramuscularly and a pediatric consultation was obtained.

Physical examination at that time revealed several scattered purplish, ecchymotic areas in the skin of the face, extremities and trunk, moderate icterus of the skin and scleras and moderate pallor of the lips and mucous membranes. The liver was palpable two fingerbreadths below the right costal margin, and the spleen was felt one fingerbreadth below the left costal margin. Examination of the blood showed a bleeding time of less than 2 minutes, an erythrocyte count of 3,900,000 and a total nucleated-cell count of 13,500, of which 31 per cent were red cells, and a hemoglobin of 16.5 gm. (Fig. 2). The icteric index

was 160. The direct blood bilirubin was 5.3 mg. per 100 cc., and the indirect 0.69 mg. There was no bleeding from the mouth or cord. Urinalysis showed no red cells, and a guaiac test on the meconium stools was negative. A blood culture was taken and was reported positive for *Staph. albus*, but a repeat blood culture made a day later was reported as negative. The maternal blood was Rh–, and the undiluted serum taken 3 days after delivery showed agglutination of one of three known Rh+, compatible bloods. Blood determinations were made daily, and on the 2nd day the nucleated-cell count rose to 26,000, with 41 per cent red cells. No more ecchymotic spots appeared on the skin, and those present gradually faded and disappeared (Fig. 2). The icteric index on the 5th day was 200. The nonprotein nitrogen was 50 mg. per 100 cc. The hemoglobin had fallen to 12 gm. and the red-cell count to 2,670,000. The urine contained large amounts of bile and the stools were deep green, presumably owing to biliverdin, with persistence of this coloration until the 10th day. Since on the 5th day respiratory embarrassment had set in, the patient was placed in an oxygen tent. Because the pallor had become more marked and the liver and spleen had increased in size, he was transfused with Rh– blood.

For the next 2 weeks the illness was severe, despite a second transfusion with Rh– blood on the 6th day. The donor was the mother of the patient in Case 1, her baby at that time being 2 months old. The icteric index increased to 600 and the hemoglobin fell to 10.5 gm. A third and a fourth transfusion with Rh– blood were given on the 8th and 10th days, and although the hemoglobin did not rise significantly and the icteric index remained at 600, the color improved. No edema of the tissues developed, and the serum protein value of the blood remained normal. The patient was removed from the oxygen tent since the respirations were no longer labored. There continued to be large amounts of bile in the urine, and the sediment showed granular casts and occasional white and red cells. The stools also contained large amounts of bile but were negative for blood, and cultures were negative for pathogenic organisms. By the 18th day the icteric index had fallen to 300 and there was improvement except for the pallor. On the 21st day, the hemoglobin was 11.2 gm., the red-cell count was 3,200,000, and because the white-cell count was rising and another blood culture was reported positive for *Staph. albus*, — a subsequent blood culture was reported negative, — a fifth transfusion was given, the blood from the original donor being used. Following this the baby again became more jaundiced. Efforts to obtain blood for a repeat icteric index were unsuccessful. The hemoglobin and erythrocyte count, which were 13.9 gm. and 4,190,000 following this transfusion, slowly dropped, but with a sixth and last transfusion the blood remained at a satisfactory level, the jaundice slowly disappeared, and the patient seemed well. During his entire stay in the hospital he was not allowed to nurse and was placed on a modification of cow's milk, water and Karo, digesting this well without vomiting.

Subsequent check-ups have shown that so far the reflexes are not hyperactive; the patient's development seems to be within normal limits, and his nutritional status is good.

At the age of eleven months this child had eight deciduous teeth, all of which had the same deep greenish discoloration as those seen in Case 1.

Discussion

It seems certain that the important life-saving factor in the treatment of these infants was the use of Rh– blood of the proper group in the early days of life. This, then, places a serious responsibility on any hospital to maintain either a current supply of Rh– blood of the various groups or a file of Rh– donors. In this connection, it might be worth while to consider some plan whereby hospitals strategically located and having blood banks, possibly those that are subsidized by the federal government under the Office of Civilian Defense, would be utilized as depots for Rh– blood. The expense of doing Rh typing on all donors might be defrayed by some state agency interested in maternal and infant welfare, and these depots would be subject to call from any hospital in the vicinity to provide the proper type of blood.

In the second case presented, it is noteworthy that the other two siblings, who showed no evidence of erythroblastosis at birth or subsequently, were both Rh+, and one may speculate that at the time of those births the development of the anti-Rh substance in the mother did not reach a sufficiently high level to damage seriously the cells within the fetal circulation. It may also be true that owing to the previous immunization to the Rh factor, the mechanism was accelerated during the third pregnancy.

From our one and a half years of experience with the Rh factor as related to isoimmunization in pregnancy, we have been led to develop a routine on all prenatal patients according to which the Rh factor and blood group are determined early in the course of the pregnancy, preferably when blood is taken for the Hinton test. If the mother is Rh–, or if there is history of erythroblastosis, stillbirths or miscarriage that suggests that isoimmunization of pregnancy may have occurred, blood is taken from the husband and siblings for determination of the Rh factor and blood group. If the mother is Rh– and the father Rh+, routine determinations of the former's serum are done biweekly from the seventh month on to determine whether any demonstrable anti-Rh substance can be found. This is performed by mixing the unconcentrated serum with a 2 per cent suspension of ten Rh+ bloods of the same blood group. If the patient's serum agglutinates a majority of these bloods when incubated at 37.5°C., the finding is taken as significant, and if possible, a titer is determined on a dilution basis. Demonstration of a significant and a rising titer is sufficient evidence to warrant prompt delivery of the infant — provided the baby is viable – to prevent excessive flooding of the

fetal blood stream with anti-Rh substance and possible intrauterine or neonatal fetal death.

The determination of the blood group serves two purposes. First, it is a matter of convenience to have the group known in the laboratory in the event that transfusions are needed in the treatment of any of the complications arising from the pregnancy. Second, since occasional cases of isoimmunization to factors other than Rh, such as the blood subgroups, have occurred and have been estimated to be responsible for 2 per cent of the cases of erythroblastosis fetalis, the determination of the blood group is important.

Demonstration of the anti-Rh substance in the breast milk[7] and the clinical impression gained by us that infants showing no evidence of erythroblastosis but whose mothers showed an anti-Rh factor in their blood stream did not do so well as expected have led us to the decision not to allow them to be breast fed until further experience has been gained in the study of a large series of cases.

Summary

Two cases of erythroblastosis fetalis of the icterus gravis type resulting from isoimmunization to the Rh factor, with apparent complete recovery, have been presented. Salient facts relative to the immediate care of the baby, with emphasis on the understanding of the mechanism of isoimmunization, have been discussed.

References

1. Levine, P., Katzin, E. M., and Burnham, L. Atypical warm isoagglutinins. *Proc. Soc. Exper. Biol. & Med.* 45:346-348, 1940. Isoimmunization in pregnancy: its possible bearing on etiology of erythroblastosis foetalis. *J. A. M. A.* 116:825-827, 1941.
2. Landsteiner, K., and Wiener, A. S. Studies on agglutinogen (Rh) in human blood reacting with anti-rhesus sera and with human isoantibodies. *J. Exper. Med.* 74:309-320, 1941.
3. Diamond, L. K., Blackfan, K. D., and Baty, J. M. Erythroblastosis fetalis and its association with universal edema of the fetus, icterus gravis neonatorum and anemia of the newborn. *J. Pediat.* 1:269-309, 1932.
4. Strong, R. A., and Marks, H. P. Icterus gravis neonatorum. *J. Pediat.* 15:658-679, 1939.
5. Diamond, L. K. Hemolytic transfusion reactions due to Rh factor: preventable danger. *New Eng. J. Med.* 227:857-862, 1942.
6. Editorial. Significance of Rh factor. *New Eng. J. Med.* 227:932, 1942.
7. Wiebsky, E., Andersen, G. W., and Heide, A. Demonstration of Rh antibody in breast milk. *Proc. Soc. Exper. Biol. & Med.* 49:179-183, 1942.

CLINICAL NOTE

OTOGENOUS INFECTION DUE TO THE PROTEUS BACILLUS

Report of a Case

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THE emphasis on the rarity and severity of otogenic infections by the proteus bacillus (*Proteus vulgaris*), expressed in a recent paper by Gerzog,[1] makes it worth while to report an additional case. According to Gerzog, previous to the case that he reports with recovery, only 9 cases had been reported in the literature since 1912. Only 1 patient survived, and this was the only case in which there was not a positive blood culture for this organism. Three patients, he states, died of meningitis and 5 of overwhelming bacteremia. The case to be reported is unique because the patient survived after having had a positive blood culture.

Case Report

C. K., a private patient of Dr. Warren W. Marston, was a 25-year-old man who had had a right chronic suppurative otitis media, with a foul odor, for most of his life but had otherwise been well. The previous year he had had a tonsillectomy, which did not change the ear condition.

On April 2, 1940, the patient began to have headache on the right side. This persisted until April 7, when he vomited all day and had a chill at night. He was sent to the Newton Hospital. On admission, the temperature was 100.2°F., rising that evening to 102.8°, and the white-cell count was 13,600, with 82 per cent neutrophils. At the first operation, performed by Dr. Donald H. MacDonald on April 9, the mastoid was opened and was found solidified with ivory-like sclerosis; a culture yielded unidentified gram-negative bacilli and *P. vulgaris*. The lateral sinus at that time was not uncovered, and the jugular vein was not ligated. For 3 days the patient was given large doses of sulfapyridine, and this treatment was followed by a temporary subsidence of the temperature.

On April 14, the temperature rose to 103.3°F. and the pulse to 120; a blood culture was reported negative. On the following morning the patient had a chill, and that afternoon the temperature rose to 103.1°F., the white-cell count being 10,700. At that time I saw the patient in consultation. Sinus phlebitis was believed to be the diagnosis, and further operation was advised. A lumbar puncture was performed on the same day, and the dynamics disclosed that the right jugular vein was blocked. On April 16 the jugular vein was ligated, the mastoid reopened and the sigmoid sinus uncovered; the mastoid antrum was reamed larger, and the dura uncovered. A liquid foul-smelling pus kept accumulating in the antrum. Following incision of the membranous wall of the sigmoid sinus, there was an escape of foul pus. A culture from this showed *P. vulgaris*, and the same foul odor was present in the culture tube. Since it was believed that the abscess was walled off within the sigmoid sinus, no further exploration was attempted; the mastoid cavity was filled with iodoform gauze, and the mastoid wound was approximated to the drain. The patient again was put on large doses of sulfapyridine.

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For the next few days, the patient ran a spiking temperature, which rose as high as 104.8°F. On April 18, the white-cell count was 45,500, with 93 per cent neutrophils. Because of continued fever, with occasional chills, and three successive blood cultures that were positive for *P. vulgaris*, it was believed that the infection must be coming from the torcular end of the right lateral sinus. Hence, on April 22 the patient was again operated on, the lateral sinus being uncovered all the way around to the torcular by removing the overlying bone of the skull. The lateral sinus itself was then opened and found filled with grayish pus all the way around to the vicinity of the torcular. Owing to the danger of pushing the last walling-off into the venous circulation on the left side, further exploration was terminated and iodoform strips were laid in the opened lateral sinus. The incision was approximated with interrupted silk sutures. Following this operation there were no more chills, and within a few days the temperature and white-cell count were normal. Subsequent blood cultures were negative, and the patient made a slow and uninterrupted convalescence.

A year later a successful radical mastoid operation aided by skin grafting was performed, which eliminated discharge and odor.

Since Gerzog's paper was published, 2 more deaths have been reported. These additional fatal cases emphasize the grave pathogenicity of the proteus organism. Even the new chemotherapeutic drugs seem to have failed to stem its serious ravages.

In 1940, Neter and Chait,[2] of Buffalo, reported the case of a fourteen-year-old girl who was operated on for chronic mastoiditis due to an infection with *P. vulgaris*. This case was complicated—by meningitis as well as by septicemia. In spite of surgery and chemotherapy the patient died on the eighth day. In 1943, Adler and Klapper,[3] of New Orleans, reported the case of a twenty-eight-year-old man with proteus infection of the mastoid. The symptoms were high fever, chills and vomiting. There was a positive blood culture for *P. vulgaris*, but no meningitis. Despite the use of sulfathiazole, sulfadiazine and finally sulfapyridine, the patient died on the twenty-second postoperative day. Autopsy revealed thrombosis of the lateral sinus, extradural abscess and a pulmonary abscess in each lung.

Summary

A successfully treated case of otogenic infection due to *Proteus vulgaris* and complicated by septicemia is reported. The pertinent recent literature is reviewed.

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References

1. Gerzog, B. G. Bacillus proteus in otogenic infections, secondary mastoiditis, thrombosis of lateral sinus and bacteremia. *Arch. Otolaryng.* 30:275-279, 1939.
2. Neter, E., and Chait, R. A. Bacillus proteus in otitis media, complicated by mastoiditis, meningitis and bacteremia. *Arch. Otolaryng.* 32:947-950, 1940.
3. Adler, H. M., and Klapper, C. Bacillus proteus septicemia accompanying acute mastoiditis with thrombosis of lateral sinus. *Arch. Otolaryng.* 37:74-77, 1943.

MEDICAL PROGRESS

THE TREATMENT OF THERMAL BURNS*

II. Recent Developments

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THIS review is intended to summarize recent developments, and supplements the general outline prepared by the National Research Council.[1] The important articles of 1943 on the fundamental concepts of burns that should be read by every physician are those by Whipple,[2] Trueta,[3] Glenn, Gilbert and Drinker,[4] Barnes and Trueta[5] and, in spite of the fact that it concerns wounds rather than burns, that by Orr.[6] The best short description of the most significant phases of local and general treatment of burns may be found in Volume V of *Military Surgical Manuals*.[7] Harkins's[8] book may be consulted for a complete résumé of the history of burns.

The articles in the medical-progress series of 1941 have been published in book form (*Medical Progress Annual*. Volume III. 678 pp. Springfield, Illinois: Charles C Thomas, 1942. $5.00).

*From the Burn Assignment of the Surgical Services of the Boston City Hospital and the Department of Surgery, Harvard Medical School.

The investigations reported in this publication were made under a contract between the Committee on Medical Research, Office of Scientific Research and Development, and Harvard University.

†Assistant professor of surgery, Harvard Medical School; visiting surgeon, Boston City Hospital; member, Subcommittee on Burns, Division of Medical Sciences, National Research Council.

Determination of Degree of Involvement of Thermal Burns

The determination of the depth of a burn is of the greatest importance, because in the past many authors have claimed that by using a given treatment a burn was maintained as a burn with destruction of only part of the epithelial cells (second degree), whereas if any other treatment had been used the burn would have been one destroying all the epithelial cells (third degree). Usually

such claims were made without any detailed description of the differentiation of the various types of burns.

A fresh burn with erythema, a moist surface, multiple broken or unbroken blisters, moderate edema of the skin and no subcutaneous edema is probably a part-thickness burn. A fresh burn with a dry, leathery, dead-white or brownish appearance is probably a full-thickness burn. But there are areas in many cases where no clear-cut diagnosis can be made early.[8-10] *The time when classification of the depth of burns should be made is after healing has occurred or successful grafting has been done.*[10] The recognition of this fact is important because the elimination of unwarranted claims, based on impossible distinctions, from serious consideration is definitely a step toward scientific thinking.

Treatment of Minor Burns

In small-area burns systemic effects such as shock can usually be disregarded. The important considerations in these cases are rapid healing, prevention of infection, minimizing of pain and reduction of disability during and after treatment.

Rate of Healing

Cannon and Cope[11] and Hirshfeld, Pilling and Maun[12] have shown that skin-graft donor sites, which are somewhat but not perfectly analogous to burns, heal much more slowly if escharotics such as tannic acid or triple dye are used than if boric acid ointment is employed. Taylor[13] has demonstrated the same thing with second-degree burns. Clowes and his associates[10] have shown that tannic acid-silver nitrate treatment delays the healing of burns. Their evidence in regard to triple dye is not so clear cut, but points in the same direction. They also found that there is a regional difference in the time of healing of burns treated by any given method, with the face healing more rapidly and the back more slowly after part-thickness burns than any other areas of the body.

Prevention of Infection

In spite of all the claims that have been made, there is no known method of keeping any burn sterile. A part-thickness burn will harbor pathogenic organisms in most cases, even when the treatment is carried out by groups specially equipped for the study of these cases.[14] Cope[15] has recently shown, however, that if a burn is dressed with a simple ointment without cleaning it, but with a bulky pressure dressing *that is left alone*, and the patient is given sulfadiazine systemically, the infection is relatively harmless. Infection has been found under the plaster casts of Levenson and Lund[16] and of Logie,[17] but serious infection in minor cases has not been reported with this treatment. Sulfanilamide and related compounds applied locally have given good results in many cases,[18] but their application in powder form may result in dangerously high levels in the blood.[17] Their local use has been bacteriologically disappointing.[14, 17] Intercurrent infection of burns at the time of dressings may be a much more serious matter than has until recently been recognized.[19] In addition to careful aseptic technic at the time of dressing, Allen and Koch,[20] Siler and Reid,[21] Owens,[22] Cope,[15] Gurd, et al.,[9] Clowes,[10] Trueta,[3] McClure[23] and Levenson[16] all stress the value of infrequent dressings as another factor in reducing the danger of infection, even though there are minor differences in their methods. Clark and his associates[19] have studied the use of penicillin and of propamidine as agents to control streptococcal and staphylococcal infections, with promising bacteriologic results. Their method, however, entailed two dressings a day, and their cases healed no more rapidly than have similar cases treated by more widely available methods. On the other hand, as penicillin becomes available in larger quantities and can be used in larger doses, it may become an extremely valuable therapeutic agent.

Prevention of Pain

The greatest cause of pain in burns is caused by friction under a dressing or by the changing of dressings. A second-degree burn should be and can be kept painless by a properly applied pressure dressing or cast from the time of first dressing until it is healed.

Reduction of Disability

Glenn, Gilbert and Drinker,[4] have shown that the subcutaneous swelling of burns of the paws can be safely prevented in dogs by the application of plaster. Levenson and Lund[16] applied this method to burned hands, and believe that the motion in burned fingers returns more rapidly to normal after this treatment than it does in cases treated by methods that do not prevent swelling. McClure,[23] in an excellent paper on the treatment of ambulatory burns, shows the value of a simple ointment dressing infrequently changed in reducing the amount of time lost from employment.

Treatment of Major Burns

When large areas of skin are burned, the situation is complicated by the systemic effects of the burn. These are, according to Wilson, MacGregor and Stewart,[24] in order of occurrence, shock,

toxemia and infection. The indefinite term "toxemia" is avoided in this review, and the various manifestations frequently discussed under it are considered separately. Shock in burns is usually caused in large part by a great reduction in the circulating blood volume, which is generally accompanied by hemoconcentration. Other complications of severe burns are, in the usual order of occurrence, hemolysis of red cells and hemoglobinuria, azotemia, azoturia, hypoproteinemia and anemia. Infection is manifested by the usual systemic signs of infection and sometimes by anemia, hypoproteinemia and weight loss.

Shock

The preventive or therapeutic treatment of shock must precede or accompany surface treatment. To treat it intelligently, the hemoglobin level or the hematocrit must be determined at the earliest moment, since changes (concentration of red cells) frequently occur long before changes in the pulse or blood pressure and may therefore give warning of impending serious collapse.

Treatment with blood plasma is by far the most valuable procedure. Saline solution, saline and glucose solution or distilled water and glucose should be given cautiously in the first twenty-four hours[25, 26] — not for the treatment of shock but to make up calculated losses of electrolyte occurring as a result of vomiting and exposure and from the collection of extracellular fluid in the burned area. Plasma was given by Cope and Rhinelander[27] in doses of approximately 500 cc. diluted with an equal amount of saline solution to each 10 per cent of surface area burned. Others[28–30] have used twice this quantity of undiluted plasma. In any case, however, repeated hematocrit determinations should be made to adjust the dosage. If hemoconcentration is present, about 500 cc. of undiluted plasma is suggested for each ten points the hemoglobin level is above 105.[7] That the treatment of shock with plasma should be started *early*, as stressed by Elkinton,[30] has been confirmed by Taylor et al.[29]

Cortin and other suprarenal substances have been extensively used in the treatment of burn shock.[9, 31] Cope and Rhinelander[27] did not find cortin useful in 2 cases. Rhoads and Lee[32] now state that further experimentation has made it impossible for them to evaluate cortin because of the inconsistent reactions they have obtained. Morphine has had a traditional and important place in the prevention and treatment of burn shock, and many authors have recommended large doses. In the unusual cases from the Cocoanut Grove disaster, it was found that large doses of morphine were harmful.[33] Even in the absence of associated pulmonary lesions, a more cautious use of this powerful drug should be made than has frequently been advised in the past. Tissue anoxia is a large factor in the harm from shock. Since morphine sedation may increase the degree of anoxia, it may be harmful.[29] Anesthesia was used by Clowes[10] in the early part of his study, as it has frequently been in the past by other workers, to permit more careful cleaning of the surface. Again, there is serious question of its safety because of the danger of increasing the anoxia. During their more recent cases, Clowes and his associates have omitted the anesthesia. As seen below in the section concerned with surface treatment, the types of treatment in which anesthesia is necessary are no longer those of choice. Although there are no new observations reported on the subject to date, the caution of Blalock[34] regarding the danger of overheating in shock should be taken seriously. The patient with a large burned area and a bulky dressing may have been deprived of more than half his normal ability to lose heat by perspiration.

Other Complications

Hemoglobinemia and hemoglobinuria have been known for many years to occur in occasional cases of very extensive deep burns. Shen, Ham and Fleming[35] have recently studied this condition and have concluded, as has Drinker[36] from animal experiments, that the hemoglobin is derived from blood cells lyzed by burning within the capillaries and other vessels of the burned skin and subcutaneous tissues. In occasional cases the excretion of hemoglobin is so rapid that damage arises from the passage of hemoglobin and from its precipitation in the kidney tubules in the usually acid urine. Repeated 4-gm. doses of alkalies (sodium bicarbonate or sodium lactate) are therefore indicated in such cases. Methods of calculating the doses are described by Levenson, Lund and Taylor.[29]

The development of hypoproteinemia a few days after a severe burn has been recognized for years. Whole-blood transfusion was the only treatment for this condition until recently, when plasma transfusion became available. Neither of these is effective for this complication unless exceedingly large doses are given. Taylor and his associates[37, 38] have shown that the use of plasma or whole blood for hypoproteinemia is impractical because of the enormous amounts that are needed to overcome the protein deficit. They found that in extreme cases 300 gm. or more of protein or the equivalent of this amount in amino acids must be given daily in addition to an ordinary high-protein

diet. To accomplish this result with plasma would require more than 4000 cc. per day.

In the first few days after a burn, a marked azotemia and azoturia[37, 38] may occur. Cope and his co-workers[39] did not find that this was severe in degree and noted little relation to the severity of the burn. Only one of their cases, however, had an area of more than 10 per cent of full-thickness skin loss. Taylor,[38] working with a much larger number of more severely burned patients, found a direct relation to the severity of the burn. This nitrogen is found both in the plasma and in the urine largely as undetermined nitrogen. There is no specific treatment for this condition, but early establishment of adequate urine output is indicated.

Anemia has always been recognized as a complication of severe burns. No treatment save whole-blood transfusion has been effective. In some cases, twenty-five or more transfusions may be needed during a period of two to six months.[27, 37]

Cope, Nathanson and their associates[39] also studied the 17-ketosteroid excretion of burned patients and found that this was depressed in inverse relation to the growth of abnormal amounts of hair on the faces and extremities of female patients. There was also cessation of catamenia for several months.

Infection

In his report of the results of work done by a large number of clinics investigating wounds and burns under the auspices of the National Research Council, Meleney[40] states, "The infection rate in burns is very disturbing, particularly in deep second and third degree cases." His statistics have not been studied in all useful aspects, but they show in general that large or deep burns have three times the incidence of serious infection that small or superficial burns have. It is difficult to estimate just what this means, because the term "serious infection" is not defined. Clowes[10] showed that all patients with full-thickness burns covering 10 per cent and over of the total surface area were infected with a mixture of organisms and were seriously ill irrespective of which one of three original surface treatments was used. His treatments were tannic acid-silver nitrate, triple dye and vaseline gauze. He also showed that part-thickness burns irrespective of the surface area involved or of the treatment had no serious infection. Full-thickness burns covering up to 10 per cent of the total surface area had numerous infections, but they were relatively easy to control.

As shown by Lyons[41] and Meleney,[40] cultures from burns usually show mixed infections. Staphylococci are almost always present in the cultures, and frequently streptococci, colon bacilli, *Pseudomonas pyocyaneus* and various anaerobes are present. No antiseptics, new or old, can control these infections for a long time, but they may reduce the toxicity and invasiveness of some of the organisms. In some cases they may improve the degree of infection enough to allow earlier skin grafting.

Surface Treatment

As indicated in the general outline of the National Research Council,[1] a strong trend away from escharotic treatments prevailed in 1941 and 1942 in the United States and Great Britain. In 1943 this trend has continued and has become more marked.

Tannic acid. Evidence that tannic acid may be toxic to the liver has been increased this year by the paper of Erb, Morgan and Farmer,[42] who studied autopsies on 61 cases. They found evidence of central necrosis of the liver in 25 of 41 patients dying after tanning, whereas no case of liver necrosis occurred in the untanned patients who died. On the other hand, they point out many real benefits that have arisen from tannic acid treatment. In a clinical paper published in the same month, Farmer[43] still advocated this treatment. One of the patients dying of burns in the Boston City Hospital in 1942 who was treated with tannic acid and silver nitrate had central necrosis of the liver at autopsy, but there was also so much pulmonary injury that the liver injury was not the only factor in the death. The British forces in the Middle East had such poor results with tannic acid treatment that they gave it up early in 1942.[17] Their difficulty, however, was infection in third-degree burns. If the alternative to tannic acid treatment were the type of ointment dressings and care given to the average case so treated a few years ago, there would be no doubt that tannic acid, in spite of the real danger of poisoning, would be the better of the two treatments. But if ointment is used with pressure dressings or casts, and if proper attention is paid to all the phases of the patient's condition, the evidence is strong that ointments are better. Clowes, Lund and Levenson[10] have presented comparative data on this and two other forms of treatment that suggest that in their series vaseline gauze or triple dye was somewhat safer than tannic acid and silver nitrate.

Triple dye. Triple dye escharotic treatment has numerous strong advocates.[44, 45] In comparison with tannic acid, an eschar is formed more slowly and usually remains slightly more flexible. In spite of the fact that the dyes are antiseptics, in-

fection always extends under these eschars when those of full-thickness burns are separating. In fact, Aldrich[44] asserts that such infected areas should be unroofed and redyed daily. This treatment was used extensively at the Boston City Hospital from 1935 to 1942 and was used on a large number of the cases from the Cocoanut Grove disaster.[10] There is no report of toxic damage to the liver as a result of the treatment, but some burns may not heal so rapidly as do those with other forms of treatment.[10]

Sulfonamide applications. Sulfanilamide, sulfathiazole, sulfadiazine and sulfaguanidine have all been used in burns in various manners. There are sprays, such as Pickrell's,[40,47] preformed membranes, such as those of Andrus,[48] Skinner[49] and Clark,[50] and ointments, such as those used by Dragstedt[18] and by Gurd.[9] Sulfonamides have also been dusted on the burn and covered with an ointment. There are reports, however, of very high blood levels with toxic manifestations when the powdered drug has been used in this manner in large-area cases.[17] Gurd[9] studied the absorption of so-called "micro" crystals of sulfathiazole from a creamy ointment in his cases, and found that high blood levels did not occur in them in spite of high tissue levels on the burn surface.

Propamidine. Propamidine is 4:4′ diamidino diphenoxypropane dihydrochloride, which is an aromatic diamidine possessing well-marked activity against various protozoal organisms as well as against the gram-positive cocci.[51] It is of interest because its action is not inhibited by para-aminobenzoic acid as is that of the sulfonamides. As yet there are no published American studies on the use of this material, but there are several British reports.[19, 52-54] To date it has been used mostly on minor burns, and the reports indicate some antibacterial activity. Healing takes place about as rapidly as with other nonescharotic treatments.

Penicillin. The only British report[19] on penicillin showed a favorable antibacterial action. The single American paper[41] was rather guarded in its claims because it was given to patients at the same time that sulfadiazine was being used.

Pressure dressings. Bulky dressings with more or less pressure are being used in major burns by Allen and Koch,[20] Siler and Reid,[21] Owens,[22] Cope,[15] Gurd[9] and Clowes.[10] Five of the six papers report cleaning of the wound before dressing it, but Cope did aseptic dressings without preliminary cleaning. In three reports, boric acid ointment[15, 20, 21] was used under the dressing, and in one each, sterile saline solution,[22] sulfathiazole ointment[9] and sterile vaseline.[10] Sulfadiazine was usually, but not always, given by mouth.

Plaster casts. Trueta,[3] Barnes,[55] Roulston,[56] Cohen,[57] Logie[17] and Levenson and Lund[16] have all used plaster casts as a primary treatment in major burns. This treatment is not new, having been previously recommended by Zeno[58] and Afonso.[59] The important experiments of Glenn, Gilbert and Drinker[4] and of Barnes and Trueta,[5] however, have placed this treatment on a firm scientific basis and have shown that the cast should fit closely and should be closed over the end of the extremity. Its most essential feature is that it prevents swelling and decreases the abnormally high flow of lymph that occurs in a limb that is not protected by a cast. Under these circumstances, the bacteria present on the surface become relatively harmless. Logie[17] says: "The three burns I was able to culture at the end of a fortnight, when the plaster of Paris was removed, grew hemolytic streptococci, and this occurred despite the usual course of prophylactic sulfonamide by mouth. But neither the patient nor the burn seemed to mind."

Secondary treatment. Any secondary treatment that entails frequent changes of dressing may expose the patient to the danger of introduction of new strains of pathogenic organisms. Owens[22] leaves his primary treatment in place for three weeks or more, and when he removes it from deep burns he wipes off the pus and débris and immediately covers the granulations with a Thiersch skin graft. In this way he avoids unnecessary contamination.

The only other relatively new secondary treatments concern the employment of new chemicals, such as propamidine and penicillin, as described above, and the use of the Bunyan[60] bag for saline irrigation. Clowes[10] found the bag useful in the few cases in which it was tried, whereas Cannon[61] did not. The trend of opinion is that infrequent dressings, simple applications and careful asepsis are the most important considerations in the surface care of burns during the time when areas of third-degree burn are being prepared for grafting.

Skin Grafting

It is easy to say that early grafting should be done, but it is sometimes extremely difficult to get the patient into condition for such grafting. Rampant infection, anemia, hypoproteinemia and possibly vitamin deficiencies[8] all prevent technically perfect grafts from taking. Clowes[10] has shown that infection per se does not prevent the success of a graft if the nutritional status of the patient is in fair balance.

The technic of skin grafting is unchanged. More emphasis is placed on early grafting to avoid the thick scars that follow late grafts. Split-

thickness grafts, sewed into place under slight tension, have almost entirely displaced Reverdin grafts in the best clinics,[7, 57] but there are a few desperately sick patients that can be grafted only by the Reverdin method.[10] The Padgett dermatome is widely used to cut split grafts. Cannon[61] successfully used an interesting type of abdominal flap very early in a case with total destruction of the skin of the dorsum of the hand and partial sloughing of the extensor tendons. In addition to Cannon's paper, the article on grafting in Volume V of *Military Surgical Manuals*[7] is extremely useful.

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References

1. National Research Council. Treatment of thermal burns. I. General outline. *New Eng. J. Med.* 229:817-823, 1943.
2. Whipple, A. O. Basic principles in treatment of thermal burns. *Ann. Surg.* 118:187-192, 1943.
3. Trueta, J. *The Principles and Practices of War Surgery with Reference to the Biological Method of the Treatment of War Wounds and Fractures.* 441 pp. St. Louis: C. V. Mosby Company, 1943. Pp. 405-413.
4. Glenn, W. W. L., Gilbert, H. H., and Drinker, C. K. Treatment of burns by closed-plaster method with certain physiological considerations implicit in the success of this technique. *J. Clin. Investigation* 22:609-625, 1943.
5. Barnes, J. M., and Trueta, J. Absorption of bacteria, toxins and snake venoms from tissues: importance of lymphatic circulation. *Lancet* 1:623-626, 1941.
6. Orr, H. W. Physiological factors involved in protecting patient against infection in healing of fractures in compound wounds. *Tr. & Stud. Coll. of Physicians of Philadelphia* 10:187, 1943.
7. National Research Council. Burns, shock, wound healing and vascular injuries. In Vol. V. *Military Surgical Manuals.* 272 pp. Philadelphia: W. B. Saunders Company, 1943. Pp. 3-103.
8. Harkins, H. N. *The Treatment of Burns.* 457 pp. Baltimore: Charles C Thomas, 1942. Pp. 2-457.
9. Gurd, F. B., Ackman, D., Gerrie, J. W., and Pritchard, J. E. Practical concept for treatment of major and minor burns: importance of timing therein. *Ann. Surg.* 116:641-657, 1942.
10. Clowes, G. H. A., Jr., Lund, C. C., and Levenson, S. M. Surface treatment of burns. *Ann. Surg.* 118:761-779, 1943.
11. Cannon, B., and Cope, O. Rate of epithelial regeneration: clinical method of measurement, and effect of various agents recommended in treatment of burns. *Ann. Surg.* 117:85-92, 1943.
12. Hirshfeld, J. W., Pilling, M. A., and Maun, M. E. Comparison of effects of tanning agents and of vaseline gauze on fresh wounds of man. *Surg., Gynec. & Obst.* 76:556-561, 1943.
13. Taylor, F. Misuse of tannic acid. *J. A. M. A.* 106:1144-1146, 1936.
14. Meleney, F. L. Study of prevention of infection in contaminated accidental wounds, compound fractures and burns. *Ann. Surg.* 118:171-186, 1943.
15. Cope, O. Treatment of surface burns. *Ann. Surg.* 117:885-893, 1943.
16. Levenson, S. M., and Lund, C. C. Treatment of burns of extremities with close fitting plaster of Paris casts. *J. A. M. A.* 123:272-277, 1943.
17. Logie, N. J. Treatment of burns at Tobruk. *Lancet* 1:609-611, 1943.
18. Allen, J. G., Owens, F. M., Jr., Evans, B. H., and Dragstedt, L. R. Sulfathiazole ointment in treatment of burns. *Arch. Surg.* 44:819-828, 1942.
19. Clark, A. M., Colebrook, L., Gibson, T., Thomson, M. L., and Foster, A. Penicillin and propamidine in burns: elimination of hæmolytic streptococci and staphylococci. *Lancet* 1:605-609, 1943.
20. Allen, H. S., and Koch, S. L. Treatment of patients with severe burns. *Surg., Gynec. & Obst.* 74:914-924, 1942.
21. Siler, V. E., and Reid, M. R. Clinical and experimental studies with Koch method of treatment of heat burns. *Ann. Surg.* 115:1106-1117, 1942.
22. Owens, N. Personal communication.
23. McClure, R. D., and Lam, C. R. Statistical study of minor industrial burns. *J. A. M. A.* 122:909-911, 1943.
24. Wilson, W. C., MacGregor, A. R., and Stewart, C. P. Clinical course and pathology of burns and scalds under modern methods of treatment. *Brit. J. Surg.* 25:826-865, 1938.
25. Tenery, R. M. Extensive cutaneous burns: with special reference to blood chemical changes. *Surg., Gynec. & Obst.* 72:1018-1027, 1941.
26. Minot, A. S., and Blalock, A. Plasma loss in severe dehydration, shock, and other conditions as affected by therapy. *Ann. Surg.* 112:557-567, 1940.
27. Cope, O., and Rhinelander, F. W. Problem of burn shock complicated by pulmonary damage. *Ann. Surg.* 117:915-928, 1943.
28. Lund, C. C., Levenson, S. M., Clowes, G. H. A., Jr., and Taylor, F. H. L. Unpublished data.
29. Levenson, S. M., Lund, C. C., and Taylor, F. H. L. Unpublished data.
30. Elkinton, J. R., Wolff, W. A., and Lee, W. E. Plasma transfusion in treatment of fluid shift in severe burns. *Ann. Surg.* 112:150-157, 1940.
31. Rhoads, J. E., Wolff, W. A., and Lee, W. E. Use of adrenal cortical extract in treatment of traumatic shock of burns. *Ann. Surg.* 113:955-968, 1941.
32. Rhoads, J. E., and Lee, W. E. Personal communication.
33. Beecher, H. K. Resuscitation and sedation of patients with burns which include the airway: some problems of immediate therapy. *Ann. Surg.* 117:825-833, 1943.
34. National Research Council.[7] Pp. 138-140.
35. Shen, S. C., Ham, T. H., and Fleming, E. M. Studies on destruction of red blood cells. III. Mechanism and complications of hemoglobinuria in patients with thermal burns: spherocytosis and increased osmotic fragility of red blood cells *New Eng. J. Med.* 229:701-713, 1943.
36. Drinker, C. K. Personal communication.
37. Taylor, F. H. L., Levenson, S. M., Davidson, C. S., Browder, N. C., and Lund, C. C Problems of protein nutrition in burned patients. *Ann. Surg.* 118:215-224, 1943.
38. Taylor, F. H. L., Levenson, S. M., Davidson, C. S., Adams, M. A., and MacDonald, H. Abnormal nitrogen metabolism in burns. *Science* 97:423, 1943.
39. Cope, O., Nathanson, I. T., Rourke, G. M., and Wilson, H. Metabolic observations [on burns]. *Ann. Surg.* 117:937-958, 1943.
40. Meleney, F. L. Study of prevention of infection in contaminated accidental wounds, compound fractures and burns. *Ann. Surg.* 118:171-186, 1943.
41. Lyons, C. Problems of infection and chemotherapy [in burns]. *Ann. Surg.* 117:894-902, 1943.
42. Erb, I. H., Morgan, E. M., and Farmer, A. W. Pathology of burns: pathologic picture as revealed at autopsy in series of sixty-one fatal cases treated at Hospital for Sick Children, Toronto, Canada. *Ann. Surg.* 117:234-255, 1943.
43. Farmer, A. W. Experience with burns at Hospital for Sick Children. *Am. J. Surg.* 59:195-209, 1943.
44. Aldrich, R. H. Treatment of burns with compound of analin [*sic*] dyes. *Maine M. J.* 28:5-7, 1937.
45. Wakeley, C. P. G. War burns and their treatment. *Practitioner* 146:27-37, 1941.
46. Pickrell, K. L. New treatment for burns. *Bull. Johns Hopkins Hosp.* 69:217-221, 1941.
47. *Idem.* Sulfonamide film for use as surgical dressing. *Bull. Johns Hopkins Hosp.* 71:304-306, 1942.
48. Andrus, W. DeW., Nickel, W. F., and Schmelkes, F. C. Treatment of burns with chemotherapeutic membranes. *Arch. Surg.* 46:1-8, 1943.
49. Skinner, H. G., and Waud, R. A. Plastic film treatment of experimental burns. *Canad. M. A. J.* 48:13-18, 1943.
50. Clark, W. G., Strakosch, E. A., and Leven, L. N. "Prefabricated eschar" or bandage, containing sulfonamide, for treatment of burns. *Journal-Lancet* 62:455, 1942.
51. Thrower, W. R., and Valentine, F. C. O. Propamidine in chronic wound sepsis: experimental and clinical study. *Lancet* 1:133-136, 1943.
52. McIndoe, A. H., and Tilley, A. R. Propamidine in chronic streptococcus infection of raw surfaces. *Lancet* 1:136-138, 1943.
53. Morley, G. H., and Bentley, J. P. Propamidine in burns. *Lancet* 1:138, 1943.
54. Kohn, F., Hall, M. H., and Cross, C. D. Propamidine at E. M. S. Hospital. *Lancet* 1:140, 1943.
55. Barnes, J. M. Treatment of burns. *Brit. M. J.* 1:408-410, 1943.
56. Roulston, T. J. Closed-plaster treatment of burns of extremities. *Brit. M. J.* 2:611-613, 1941.
57. Cohen, S. M. Experience in treatment of war burns. *Brit. M. J.* 2.251-254, 1940.
58. Zeno, L. Tratamiento de las quemaduras simples y complicadas mediante el enyesamiento. *Arch. urug. de med., cir., y especialid.* 14:322-324, 1939.
59. Afonso, J. Tecnica de Zeno para o tratamento das queimaduras. *Arq. brasil de cir. e ortop.* 6:302-309, 1938.
60. Bunyan, J. Envelope method of treating of burns. *Proc. Roy. Soc. Med.* 34:65-70, 1940.
61. Cannon, B. Procedures in rehabilitation of severely burned. *Ann. Surg.* 117:903-910, 1943.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 29481

PRESENTATION OF CASE

A six-and-a-half-year-old boy entered the hospital for study.

The patient was a full-term, normally delivered infant, who failed to gain in weight after the sixth month. Five and a half years prior to entry, at the age of one, he developed "pneumonia of the right lung," for which he was hospitalized in Nebraska. Shortly after this hospitalization he developed bilaterally discharging ears and "mastoid infection," but no operation was performed. He remained in a hospital for three years, during which period he had recurrent episodes of acute dyspnea with cyanosis and marked breathlessness and signs of fluid in the right chest. He was tapped at least six times during the three-year period, each time with the removal of 500 to 600 cc. of fluid. The fluid was "opalescent in the early stages and contained bodies that resembled typical Blastomyces, but no budding was seen." It was not known what the cultures showed. There was some pain in the right lower chest, and slight cough but no productive sputum. X-ray studies during that time showed "lack of aeration of the lower and middle lobes of the right lung." Bronchoscopy revealed "a markedly stenosed, contracted, dry bronchus to the lower lobe." In another hospital in the same state, he was given a series of x-ray treatments to the chest without any improvement.

During the next two years the boy's health improved considerably. He had no chest taps but developed progressive shortness of breath so that he became "blue" on exertion. About one month prior to admission he was seen in a community hospital where x-ray films, following the injection of lipiodol, were said to have shown slight increase in aeration of the right upper lobe but complete atelectasis of the right lower lobe. Bronchoscopy at that hospital was "difficult because of a markedly stenosed and dry bronchus leading to the lower lobe, beyond which the lipiodol was unable to go."

There was no fever, chills, night sweats, cough, hemoptysis or chest pain. The boy's appetite had remained good. His weight gain averaged 3 to 4 pounds a year. There was no nausea, vomiting, abdominal pain, dysuria or hematuria. Aside from the slow weight gain, his development seemed to be normal. Two tuberculin tests performed about three years apart were negative.

Physical examination on admission showed a pale, frail-looking boy in no distress who appeared to be chronically ill. There was marked asymmetry of the chest. The right side was flattened and moved but little with respiration. The left side was rounded and moved fully with respiration. The heart was displaced to the right. Its right border was 2 cm. to the right of the sternum. The left border of cardiac dullness was 4 cm. to the left of the midsternal line. The sounds were of good quality and regular. Below the right scapula posteriorly there was dullness to flatness with absent breath sounds, whispered and spoken voice and tactile fremitus. No rales were heard. The left lung was clear. The border of the liver was palpable three fingerbreadths below the costal margin. The spleen was not felt, and no tenderness or masses were palpable. The rectal examination was negative. There was no clubbing of fingers or toes.

The blood pressure was 100 systolic, 60 diastolic. The temperature was 98.6°F., the pulse 100, and the respirations 20.

Examination of the blood showed a red-cell count of 4,700,000, with 95 per cent hemoglobin. The white-cell count was 9000, with 52 per cent neutrophils, and 44 per cent lymphocytes. The urine was normal. A blood Hinton test was negative.

X-ray examination of the chest showed a well-defined mass in the lower portion of the right chest posteriorly surrounded by flecks of opaque material, some of which resembled lipiodol while others simulated calcification. The opaque material extended far below the level of the left diaphragm. There was probable atelectasis in the lower portion of the right lung.

Plain films of the abdomen revealed a dumbbell-shaped area of increased radiolucence in the right side of the abdomen, extending from the tenth rib down to the level of the fourth lumbar vertebra. In the region of the isthmus of the dumbbell there was a group of unusual areas of calcification that had the appearance of small bones and possibly incomplete teeth. On the lateral view this whole area appeared to be posterior, approximately in the position of the right kidney but occupying a much larger space and replacing the liver anteriorly.

"Review of the x-rays taken in Nebraska showed a similar mass on the films taken at six months of age. The mass had grown approximately with

*On leave of absence.

the growth of the patient. Some areas of calcification were seen on the old films outside the area of radiolucence in the region where the lower portion of the lipiodol was at the present time."

An intravenous pyelogram showed prompt excretion of dye filling a normal left kidney pelvis and ureter. The right pelvis was markedly displaced laterally and somewhat posteriorly by the tumor mass previously described. The kidney pelvis and the uppermost portion of the right ureter were dilated. On the right side no filling of the ureter was seen beyond the uppermost 2 cm.

A gastrointestinal series showed the stomach to be displaced to the left and slightly anteriorly. Some direct pressure was noted on the second portion of the duodenum. The displacement of the stomach, however, was greater than could be explained by the mass itself and was probably due to a displaced liver. A barium enema was negative. The bone development was normal.

During the next forty days the boy showed an almost daily afternoon rise of temperature to 100°F. A right thoracentesis performed on the thirteenth day gave thin watery nonodorous fluid with some fibrin particles and, at the end, blood-culture and guinea-pig inoculation of the material were negative. No tumor cells were seen in the smear.

On the fortieth hospital day an operation was performed.

Differential Diagnosis

Dr. Ralph Adams*: Perhaps we should see the x-ray films first.

Dr. Laurence L. Robbins: These three films of the chest were taken at the community hospital where all the attention was centered on the chest because of the previous story. There is evidence of a mass apparently in the posterior portion of the right lower chest, and the heart and mediastinum are displaced somewhat to the right. These are the flecks of increased density. I cannot tell which is lipiodol and which is calcification. This is a film taken after lipiodol injection at the community hospital; it shows incomplete filling of the bronchi of the lower lobe on the right. After the patient had been here for a while, we received these chest films, which were taken when the boy was approximately six months of age. It was then possible to see this calcification or, if you wish, ossification in the right upper abdomen, which was present at that time. That led to further investigation of the mass in the abdomen. As you will notice, there is a large area of radiolucence, which could easily have been mistaken for gas at the first examination of the film, but it is always constant in this position and it is an unusual place for a gas-filled viscus. The liver is displaced forward. The right kidney is displaced, and there is evidence of hydronephrosis. The stomach and duodenum are displaced to the left.

Dr. Adams: I recently saw a patient with extensive bronchiectasis, gallstones, a bleeding uterine fibroid and thrombophlebitis who successfully defied the old axiom that one should be able to make one etiologic diagnosis to explain all the symptoms of a patient. On the first reading of this record, it seemed that a "complication of diseases" should be the conclusion. After study I think that a single explanation of the findings can be offered.

The first omen of illness apparently appeared at six months of age, when the child ceased to gain weight normally, but this evidence is not definitive. "Pneumonia of the right lung," occurring at one year, is a lead toward localization of disease, but it could be pneumococcal or nonspecific, lobar or bronchiolar, or an example of loosely used terminology. This episode related to the lung, plus the fact that he shortly developed bilaterally discharging ears and a mastoid infection, means that his principal and accessory air passages had been victims of an assault by virulent infection or that these passages were too poorly constituted to withstand ordinary stress and strain. The boy remained sick enough to receive hospitalization for three years, and had fluid withdrawn frequently from the right chest, but it was not pus as it should have been if it were due to a complication of the so-called "pneumonia." If uninfected pleural fluid were present before the onset of real pneumonia it would almost surely have become infected as a sequel to it. This not being true, I am assuming that the fluid was of extrapulmonary origin and that the accessory air-passage disease was a reflection of faulty development.

Again referring to the fluid, it was "opalescent in the early stages and contained bodies that resembled typical Blastomyces, but no budding was seen." That is only another way of saying "no budding, no blastomycosis." The examiners no doubt confused the swollen mesothelial cells often seen in fluid under pressure with Blastomyces. A slight cough without productive sputum is characteristic of pulmonary compression by pleural accumulations, whether air, clean or infected fluid, or solid masses. Pulmonary compression, rather than pulmonary infection, is proved by the x-ray and bronchoscopic findings of "lack of aeration of the lower and middle lobes of the right lung," and "a markedly stenosed and dry bronchus lead-

*Surgeon, Lahey Clinic.

ing to the lower lobe." In other words, this child had an atelectatic lower lobe without infection in the bronchi or in the pleural fluid surrounding the atelectatic lobe, and neither could be true if the atelectasis were secondary to intrinsic bronchial obstruction or infection, as productive bronchiectasis and empyema would surely have followed. Also, the collapsed lobe was in the midchest rather than in the posterior gutter, where intrinsically collapsed lower lobes are found. The final clue to the reason for compression atelectasis is given in the x-ray demonstration of a well-defined mass in the posterior portion of the right chest.

The differential diagnosis on admission of the patient to this hospital, at the age of six and a half, after an illness of at least six years, should furnish the answer to three simple questions: What kind of tumor was it? Where had it originated? and Why?

By exclusion, it was not a tuberculous abscess because of two negative tuberculin tests and no signs of tuberculosis elsewhere in the body. It was not a pyogenic abscess because all indications of systemic reaction to pyogenic infection were lacking. It was not a lesion of the adrenal gland because the blood pressure was normal and it had grown too large.

This lesion had grown in such a location and tissue plane that it pushed the liver and duodenum forward and to the left, the hepatic flexure downward and to the left and the right kidney downward and backward and that it penetrated the diaphragm and collapsed the lower right lung, displacing it forward and to the left. In other words, it lay in the right paravertebral gutter and in the retroperitoneal tissue plane.

The retroperitoneal tumors in this location that must be considered in this case include only the group derived from tissue elements of the embryonal urogenital ridge. They are carcinoma and hypernephroma of the kidney, embryoma, Wilms's tumor, ganglioneuroma and teratoma. Except for passive hydronephrosis from positional displacement, the data of the case afford no evidence of renal disease and establish the fact that the tumor had existed for five and a half years. For these two reasons carcinoma and hypernephroma of the kidney are untenable diagnoses.

Every feature of this lesion classifies it as an embryoma, using the term in its strict dictionary meaning of a tumor derived from embryonal structures. I should perhaps refresh your memory that the embryonal structures are those which exist during the embryonal stage, and that this stage refers to the product of conception from the end of the second to the beginning of the eighth week of its intrauterine existence. Such tumors tend to grow to enormous size, to show calcification within their substance, as a result of hemorrhage infection or necrosis, and to usurp by displacement and pressure rather than invasion the space allotted to normal organs. Derived from embryonal tissue, they possess the abortive but nevertheless potential growth capacities of the three primordial germ layers, and express the attempt to produce organ facsimiles of their host with variable completeness of frustration and confusion. Any tissue may be represented except true genital cells. Ganglion cells are frequently numerous, and if nonmedullated, irregularly coiled masses of nerve fibers predominate, the tumor is given a subname of ganglioneuroma. If renal and striated muscle cells fill the pathologist's microscopic section and the host, usually a child, has died within two years from metastasis of a carcinoma developing in some point of the tumor epithelium, it is called a Wilms's tumor. This is not, therefore, a Wilms's tumor. If the specimen includes developmental products of independent or aberrant germ cells recognizable as rudimentary organ masses, it is called a teratoid tumor or teratoma. It would be futile for me to try to classify this tumor beyond the term embryoma.

If analogy from experiments on parthenogenesis in frog ova, asymmetry reversal in Patiria blastulae, polyembryony in nine-banded Armadillo ova, and deductions from human instances of situs inversus, twinning and monstrosity are correct, tumors of this sort result from temporary disruption of normal intrauterine environmental factors at a critical period of development, whereby a mass of embryonal cells is separated from its fellows, and later produces an embryoma through parasitic growth.

DR. EDWARD B. BENEDICT: How do you explain the lesion involving the chest as well as the abdomen?

DR. ADAMS: I[1] reviewed this subject six years ago and I have not had a chance to look into it since. Mall,[2] MacCallum,[3] Newman[4] and notably Bosaeus[5] described tumors such as this, and in the lower animals those arising from the urogenital ridge often occupy both pleural and abdominal cavities. I think this tumor has expanded through the diaphragm.

DR. BENJAMIN CASTLEMAN: Do you want to go any farther and say whether you think the tumor is benign or malignant?

DR. ADAMS: I have gone quite far already. If it is an embryoma in the strict sense of the word or, to specify further, if it is a teratoma, it is a benign lesion; but having the three primordial germ layers originally present, it could become malignant. MacCallum had a patient with true teratoma who finally died of metastases, and it

was found post mortem that the metastasis was from a carcinoma that had developed within the teratoma and that blood-vessel emboli were the source of the metastatic growth.

DR. CASTLEMAN: Such a condition is occasionally found in the ovary and in teratomas, that is, the part that becomes malignant is usually the epithelial element.

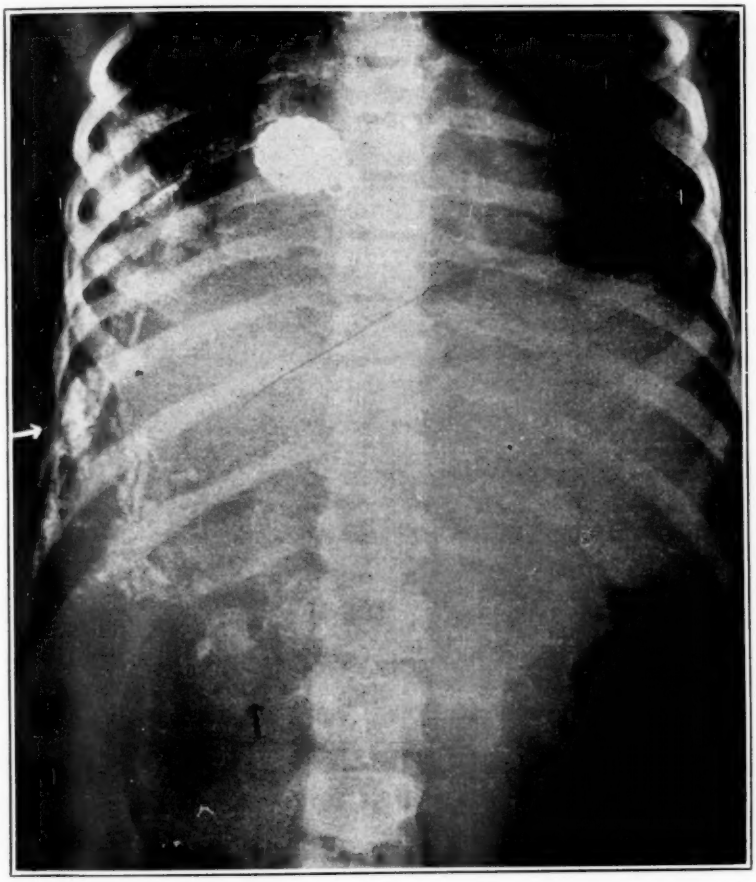

FIGURE 1. *Roentgenogram of Chest and Abdomen.*

The upper arrow points to the lipiodol injected into the mass within the chest; the lower arrow, to areas of calcification within the area of radiolucence.

DR. ADAMS: This tumor had not been malignant during the six known years of growth. I do not know how I could say whether eventually it showed malignancy in some one of its parts.

DR. RICHARD H. SWEET: I should like to say that it took us forty days to come to the conclusion that Dr. Adams has reached in a few minutes. I must confess that our approach was not so philosophic and certainly not so poetic; in fact it was very practical because I wanted to know where to make my incision. It turned out that if we had gone into the chest primarily, we should have been in trouble; if we had gone into the abdomen primarily, we should also have been in trouble.

We waited forty days and decided ahead of time to go into both places. An incision was made between the scapula and the spine, down through the ninth interspace, across the costal margin into the right rectus sheath and down the rectus sheath to a point below the level of the umbilicus. The abdominal portion of the incision was opened first, and the tumor was found lying retroperitoneally between the kidney and the liver. On incising overlying peritoneum, it was soon discovered that the tumor passed directly through the diaphragm. The incision was therefore enlarged by dividing the eighth, seventh and sixth ribs posteriorly. The attachments of the tumor to the diaphragm were then divided and the abdominal portion was freed. It was most adherent to the sides of the vertebras, at which point great care had to be exerted to avoid the vena cava. There were several large branches of the intercostal ar-

teries going directly onto the tumor at this point. After freeing the abdominal portion and dividing the rim of diaphragm that surrounded the tumor, the dissection was carried up within the chest where the tumor was found to be cystic. That is what had been tapped all these years. The largest portion of the tumor lay within the chest, and it was adherent to the parietal pleura, to the undersurface of the right lower lobe of the lung and to the pericardium. All adhesions were separated by blunt dissection without much difficulty. The tumor was finally removed in one large dumbbell-shaped mass.

Clinical Diagnoses

Tumor of chest (? cyst).
Dermoid cyst of abdomen.

Dr. Adams's Diagnosis

Embryoma of retroperitoneal space, with extension through the diaphragm into the chest.

Anatomical Diagnosis

Dermoid cyst of chest, abdomen, retroperitoneal space and postero-inferior mediastinum.

Pathological Discussion

Dr. Castleman: This tumor was filled with large amounts of sebaceous material; the wall was in places hard, fibrous and cartilaginous, and in other places calcified and ossified. It had all the characteristics of what we ordinarily call a dermoid cyst or that type of embryonal tumor that is made up for the most part of skin, sebaceous glands, hair follicles, calcium, cartilage and bone, and that fits in with Dr. Adams's diagnosis of embryonal or teratoid tumor.

The patient went back to Nebraska and is now well, four months after discharge.

References

1. Adams, R., and Churchill, E. C. Situs inversus, sinusitis, bronchiectasis: report of five cases, including frequency statistics. *J. Thoracic Surg.* 7:206-217, 1937.
2. Mall, F. P. Study of causes underlying origin of human monsters. (Third contribution to study of pathology of human embryos.) *J. Morphol.* 19:3-367, 1908.
3. MacCallum, W. G. *A Textbook of Pathology.* Fourth edition. 1177 pp. Philadelphia: W. B. Saunders Company, 1929. P. 1094.
4. Newman, H. H. Experimental analysis of asymmetry in starfish, Patiria miniata. *Biol. Bull.* 49:111-138. 1925. Studies on human twins: methods of diagnosing monozygotic and dizygotic twins. *Ibid.* 55:283-297. 1928.
5. Bosaeus, W. *Beiträge zur Kenntnis der Genese der Ovarialembryone: experimentelle Untersuchungen über parthenogenetische Ovarialgravidität bei Amphibien.* 303 pp. Uppsala: Almqvist and Wiksells, 1926.

CASE 29482

Presentation of Case

A forty-one-year-old unmarried woman, a factory worker, entered the hospital because of pain and marked swelling in the left foot.

At the age of seven years the patient developed multiple bony swellings usually preceded by "hot and searing" pain. From about the age of fourteen her general growth and physical development appeared considerably retarded. Slow growth was also noticeable in the various bony swellings to such an extent that the onset of a tumor in her finger, which at the time of entry markedly interfered with her activity, could not be remembered. The swellings, however, were always preceded by the sensation already described. Six years before entry she noticed weakness in the left ankle. This was followed in a few weeks by the hot-and-searing sensation. A small fusiform swelling appeared on the distal part of the tibia, which progressed slowly. One year prior to admission the swelling in the ankle became quite large and painful. She was admitted to a community hospital where x-ray films were taken and the tumor was removed. About six months later the swelling in the left ankle recurred and became more painful.

Her mother was said to have had "arthritis" in one knee. Five brothers and one sister were well developed and of normal height.

Physical examination showed a dwarfish woman, who was 52 inches tall. There was a left total curve of the spine. The right scapula was lower and more prominent than the left. The spinal motions were "good." There was considerable flaring of the right costochondral margin, and atrophy of both pectoral muscles. Multiple small nodules were present on the distal ends of the right radius, ulna and proximal phalanx of the thumb. Similar nodules were present in the middle phalanx of the left middle finger and in all the phalanges of the fifth finger. There was only minimal motion of the interphalangeal and the metacarpophalangeal joints but full range of motion in the other joints. The right anterior superior spine and the iliac crest were much more prominent than those on the left. A nodule was palpable in the right iliac crest. On the medial aspect of the left ankle, extending anteriorly and over the lateral side, with considerable gross deformity of the foot, was a mass about 10 cm. in diameter, which was hard and covered with tensely stretched, warm, slightly reddened skin. There was no motion in the left ankle. There were multiple small nodules on the left tibia and the lower aspect of the left femur, the phalanges of the second and third toes, and the adjacent metatarsal bones. The right lower extremity showed posterior bowing of the fibula, with multiple small palpable "bony masses" on the proximal aspect of the tibia and a small one on the distal portion of the femoral shaft. There were many small nodules on the phalanges of all the

toes of the right foot. The ankle motion was normal.

The blood pressure was 120 systolic, 50 diastolic. The temperature was 98.6°F., the pulse 86, and the respirations 20.

Examination of the blood showed a red-cell count of 3,860,000, with 70 per cent hemoglobin. The white-cell count was 5500. A blood Hinton test was negative. The urine sediment contained 10 epithelial cells per high-power field, and the urine gave a ++ Sulkowitch test for calcium. The sedimentation rates were 2, 12, 23 and 32 mm., respectively, at fifteen-minute intervals. The blood calcium was 10.5 mg., the phosphorus 3.8 mg., and the phosphatase 6.4 Bodansky units per 100 cc.

X-ray examination showed the bones of the lower legs to be shorter than normal. At the ends they were irregularly widened with multiple cyst-like expanding lesions. The bone structure at the ends of bones was irregular, and there were numerous areas of calcification. The lower end of the left tibia was irregularly destroyed, and there was a grapefruit-sized soft-tissue tumor with areas of calcification and bone fragments within it that replaced the os calcis and talus (Fig. 1). There were numerous cyst-like expanding lesions in the bones of the hands (Fig. 2). A lateral film of the skull showed a cyst-like area projected on the sella, but no other significant findings were present. There were no metastatic lesions in the chest; the costochondral junctions were irregular and widened with areas of calcification in poorly defined rib ends, which merged with the calcified costal cartilages.

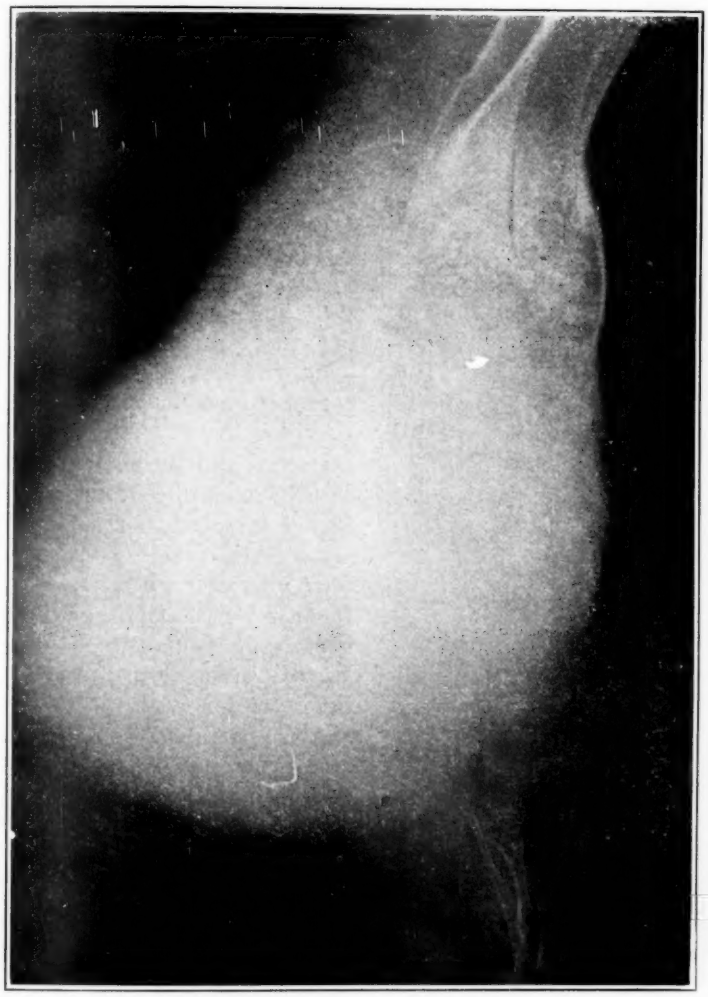

FIGURE 1. *Roentgenogram of Left Ankle.*

On the third hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. WILLIAM BECKMAN: The essential features of this case — the bony nodules or lumps on the bones that developed progressively from child-

hood and were still developing at the age of forty-one, the short stature of the patient and the deformity of the skeleton, that is to say the bowed legs and the curved spine — constitute a syndrome that has been well recognized by the medical profession since at least the late eighteenth century. This is a syndrome called by many names, of which the commonest are multiple cartilaginous exostosis and multiple enchondromatosis. The way I was able to make the diagnosis was to take the x-ray films and look through an x-ray textbook until I encountered other ones like them. Then there was no question that it represented a characteristic syndrome. I think that Dr. Schulz might describe the x-ray findings at this time.

FIGURE 2. *Roentgenogram of Left Hand.*

DR. MILFORD SCHULZ: Primarily, this patient shows a dysplasia of chondral bone growth. That portion of the bone involved in periosteal and endosteal growth is not particularly disturbed, but where this meets the epiphysis there is disruption of the normal character of the bone. These portions are wide, short and deformed. Here in the chest the costochondral junctions show severe deformities with irregular areas of calcification within them. These lesions in the hands, of course, are quite characteristic of multiple enchondromas. You might be interested in seeing the films that were taken at the community hospital six years before entry. There was then only a small amount of calcification in the soft tissues around the ankle. Now the talus and calcaneus are destroyed, and the tumor has involved and destroyed the lower end of the tibia.

DR. BECKMAN: Another feature of this disease is that the bones are affected irregularly. That is particularly apparent in this case if you compare the metacarpal bones in the two hands. It can be seen that the corresponding bones are not always of the same length.

I have tried hard to work out a differential diagnosis because that is what one is supposed to do at these exercises; but it is difficult because there is nothing else that looks like this. I found one case that had been confused with hyperparathyroidism, but certainly this could not be considered here, particularly since there was no alteration in the blood chemistry.

Honeij[1] did metabolic studies and found that patients with the syndrome under consideration excrete more calcium on a low-calcium diet than an ordinary person does; but these experiments were repeated by Sanderson and Smyth[2] who found no deviation from normal. Hence, there is probably no disorder in the calcium metabolism. In 1917 a report by Ehrenfried[3] from the Children's Hospital states that there were 600 cases in the literature at that time. Thus it is not so rare a condition as it might seem. The disease is usually hereditary, and in one family of seventy-six members, twenty-two of them were afflicted. This patient knew of no signs of the disease in any of her family so the hereditary aspect was not present, which is true in about one third of the reported cases.

One significant clinical datum was omitted when they did not tell the duration of the chief complaint but I assume from the story of the present illness that it was probably six months or so. At any rate it is quite evident that something different was going on in the left ankle.

It is unusual to have pain in benign tumors, and although this patient always had pain, it never bothered her enough to go to a hospital. Then, because of severe pain in the ankle she sought medical advice. The tumor in the ankle was also different because it grew much faster than the others, and six months after removal it had recurred. Also, the soft-tissue reaction around the ankle with redness and heat was different

from the changes observed during the development of the other swellings. Furthermore, she had evidence of constitutional disease, as shown by an elevated sedimentation rate and anemia. She also had a slightly elevated phosphatase, which suggests that osteoblastic activity was vigorous. I believe that one of the enchondromas in the left ankle had become malignant and that an amputation was performed.

DR. BENJAMIN CASTLEMAN: When you say "enchondromas," are you making any distinction between osteochondroma and enchondroma?

DR. BECKMAN: No, although I probably should have. Both are present in this disease. You can see all sorts of little ones in the phalanges — enchondromas and exostoses.

DR. CASTLEMAN: Dr. Schulz, will you comment on that? Are these tumors osteochondromas or enchondromas? I think there is a definite distinction.

DR. SCHULZ: I do not know whether one can classify them as exostoses or enchondromas. Those in the hands, of course, are quite characteristically enchondromas.

DR. GEORGE W. HOLMES: I believe that it would be possible for enchondroma to be responsible for the entire picture. A central tumor producing a local expansion of the bone might be projected in such a manner that it would appear to be partially outside the bone. Radiologically the only difference between an enchondroma and an osteochondroma is the location.

CLINICAL DIAGNOSES

Chondrosarcoma of tibia.
Multiple enchondromatosis.

DR. BECKMAN'S DIAGNOSES

Chondrosarcoma of tibia.
Multiple cartilaginous exostoses.
Multiple enchondromatosis.

ANATOMICAL DIAGNOSES

Chondrosarcoma of tibia.
Multiple enchondromatosis.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: There has been a lot of misunderstanding concerning these two diseases.

DR. WALTER BAUER: "Loose talk" is a better term.

DR. CASTLEMAN: First let me define some of the terms that we are all agreed on. We use the terms "exostosis" and "osteochondroma" interchangeably because these tumors appear to project out from the bone and because they are usually composed of both bone and cartilage. These tumors may be either single or multiple, and when multiple the disease is usually hereditary and called "multiple cartilaginous exostoses" or what Jaffe[4] in a recent paper prefers to call "hereditary multiple exostoses." Pathologically exostoses may be predominantly cartilaginous or osseous, and occur almost always in the vicinity of the epiphyseal cartilage. According to Jaffe they are covered with periosteum and their outlines are really irregularly outpouched cortex; they are not superimposed on the cortex.

An enchondroma is a cartilaginous tumor inside the bone, often occurring close to the epiphysis, but not necessarily. These tumors may also be single or multiple, and when multiple the condition is often called "multiple enchondromatosis" or, according to Ollier,[5] "dyschondroplasia." This disease is not hereditary and is sometimes called Ollier's disease. Some of the confusion between this condition and multiple cartilaginous exostoses is due to the fact that Ollier[6] also published a paper on the latter disease. Ollier, however, made a definite distinction between the two. There is no definite evidence that combinations of the two conditions have occurred in the same patient.

DR. BECKMAN: Ollier described a unilateral disease; Ewing,[7] however, makes no differentiation between Ollier's disease and the condition present in this patient.

DR. CASTLEMAN: It is true that Ollier first described it as unilateral, and for that reason disease involving both sides was formerly not called Ollier's disease. Usually the lesions are only on one side, but there have been a number of cases reported in which they occurred on both sides. Even Ollier's own students[8] described them on both sides.

This patient's foot was amputated about 8 cm. above the ankle. The tumor was composed of cartilaginous nodules, and microscopic examination showed it to be a chondrosarcoma. In addition many of the phalanges away from the tumor were almost completely replaced by enchondromas. No exostoses were found. I believe, therefore, that this is a case of multiple enchondromatosis with sarcomatous degeneration of one of the lesions in the lower end of the tibia.

REFERENCES

1. Honeij, J. A. Study of multiple cartilaginous exostosis. *Arch. Int. Med.* 25:584-627, 1920
2. Sanderson, G. H., and Smyth, F. S. Chrondrodysplasia (Ollier's disease): report of case resembling osteitis fibrosa cystica. *J. Bone & Joint Surg.* 20:61-67, 1938.
3. Ehrenfried, A. Hereditary deforming chondrodysplasia — multiple cartilaginous exostoses: review of American literature and report of twelve cases. *J. A. M. A.* 68:502-508, 1917.
4. Jaffe, H. L. Hereditary multiple exostosis. *Arch. Path.* 36:335-357, 1943.
5. Ollier, L. De la dyschondroplasie. *Bull. Soc. de chir. de Lyon* 3:22-24, 1900.
6. *Idem.* Exostoses ostéogéniques multiples. *Lyon méd.* 88:484-486, 1898.
7. Ewing, J. *Neoplastic Diseases: Treatise on tumors.* 1160 pp. Philadelphia and London: W. B. Saunders Company, 1940. P. 204.
8. Molin, H. *La dyschondroplasie: étude radiographique et clinique.* 124 pp. Thèse de Lyon. 1900.

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THE HEALTH OF THE NATION

During the one hundred and fifteen years of its existence, the *Journal* has witnessed many changes in medical and public-health practices in the United States, all of which have been directed to the ever-present responsibility of the medical profession — the improvement of the health of the people.

Medical research has steadily advanced knowledge concerning the cause, prevention and treatment of disease. Drugs such as arsphenamine, insulin, liver extract, the sulfonamides and penicillin have been shown to possess phenomenal curative effects. Morbidity and mortality rates have declined to figures that, only twenty-five years ago, would have been considered fantastic. Certain communicable diseases, such as smallpox, typhoid fever and diphtheria, have been practically eliminated as health hazards. Undergraduate and postgraduate medical education has improved to such an extent that it is unequaled in any part of the world. Hospital facilities in most regions of the country are adequate, regarding both number of beds, trained personnel and equipment.

Other factors that are indirectly concerned with the practicing physician have contributed to the improved health of the people. Measures promoted by public-health departments, such as sanitation, quarantine, tuberculosis case-finding and immunizing methods, have played a significant role, particularly in the control of communicable diseases. The creation of boards and colleges of specialists has led to the recognition of those who are properly qualified in their particular fields. Nationwide programs have done much to educate the population concerning medical matters, and in the majority of states opportunity for budgeting the costs of hospital or medical care, or both, is available.

In spite of all these things that are directly or indirectly concerned with the practice of medicine, a number of nonmedical conditions have influenced the health of the Nation. Among these should be included good wages, a high standard of living, unsurpassed educational facilities, excellent means of transportation, and well-endowed and well-administered charitable organizations.

The total result has been a nation as healthy as, if not healthier than, any other nation in the world, and one whose health is constantly improving, and yet the people of the United States and the medical profession are now faced with a proposed legislative act — the Wagner-Murray-Dingell Bill — that purports to promote an even healthier population by the federalization of many of the activities that have been responsible for the advances of the past and that, by and large, have been the direct result of the essence of democracy — individual enterprise and effort.

Within the past two months officially appointed representatives of the state medical societies of New England have jointly considered what steps should be taken regarding this epitome of bureaucracy. The group drafted a statement con-

cerning the proposed legislation, which is printed elsewhere in this issue of the *Journal*. The statement has been approved by the appropriate executive bodies of the state medical societies, and on December 2, copies were forwarded to each senator and representative in Washington by the medical society of his respective state.

The gist of the statement is a plea for the utilization by the states of existing voluntary agencies, if necessary with the assistance of federal grants-in-aid. In other words, it seems likely, if not inevitable, that federalization of medical and hospital care and of medical education and research would destroy the very foundation on which the health of the people of the United States is based. Certainly the threat is so ominous that every physician should explain to his patients and friends what agencies and philosophies have been responsible for the advances of the past, how these would be affected by the Wagner–Murray–Dingell Bill, and how such uncontrolled and radical experimentation can be avoided.

POSTWAR TUBERCULOSIS CONTROL

The foundation for ending tuberculosis in the United States, and for its control in all the world, is now being laid in wartime by the United States Public Health Service and the National Tuberculosis Association. The outlook for success is good. This is in face of the fact that, in long wars, tuberculosis has been a prime factor in raising the general death rate. The rise already has come in Europe. Its first signs appeared this spring in the United States, where the general tuberculosis death rate still was falling, but where an upturn came among the young. The small American setback had an ominous counterpart in Europe, where children were affected much more than adults, particularly by the nonpulmonary types of the disease. In England and Wales, deaths among children under ten years of age from all forms of the disease increased 45 per cent during 1941 over the 1939 figure, as compared with a 12 per cent increase for the general population. In Paris during the same period, the death rate among children from one to nine rose 28 per cent, as against only a 10 per cent increase for the general population. This shows the insidious ways of tuberculosis and the magnitude of the job, because, when this war started, it was expected that those to be the hardest hit would be not British children but young women war workers, who were the foremost victims in World War I. An explanation suggested for the plight of American children is their mothers' diversion to war work.

In World War I, in Germany the tuberculosis death rate rose 61 per cent, in Italy 44 per cent, in England 42 per cent and in the United States 6 per cent. Authentic reports from Germany and Italy have not been available since the start of World War II. Meager reports from France show that deaths from tuberculosis have increased. But England held her increase in deaths from the disease to about 12 per cent during 1940 and 1941, and during 1942-1943 the number of deaths dropped to the 1938 level, which is the lowest on record. The tuberculosis death rate in the United States during a period lacking only a few months of the duration of her participation in World War I was still dropping. The 1941 death rate was an all-time low of 44.4 per 100,000, was probably about 43 for 1942, and this year will undoubtedly be still lower.

There are many angles behind this hopeful side, but the main weapon by which Americans propose to drive tuberculosis from the land is increasing use of x-ray films of the chest. The Selective Service boards and induction stations employ it on draftees, and state after state, and county after county, are following up the men deferred or rejected on account of tuberculosis. The United States Public Health Service and state tuberculosis organizations are extending the use of such films to war industries, and the same follow-up to promote medical care is used as in draftees. Furthermore, the Public Health Service is extending its offer of service to families of workers found to be tuberculous, and the War Emergency Committee of the National Tuberculosis Association has recommended to local tuberculosis associations many measures, including special attention to women employees and to emergency housing conditions.

Tuberculosis is coming to light in a great sector of the population where it was never before searched out on a large scale. The magnitude amounts to something new in this great health battle. The momentum here and in England promises success for the international postwar control activities now planned by the United States Public Health Service and the National Tuberculosis Association. Certainly the annual Christmas Seal Sale, the proceeds of which provide substantial support to this program, deserves the enthusiastic support of every physician!

MEDICAL EPONYM

Libman-Sacks Syndrome

Emanuel Libman (b. 1872) and Benjamin Sacks (b. 1896) are the authors of a paper, entitled "A Hitherto Undescribed Form of Valvular and Mural Endocarditis," appearing in the *Transactions of the Association of American Physicians* (38: 46–61, 1923). This same article also appeared in the *Archives of Internal Medicine* (33: 701–737, 1924). A portion of the discussion follows:

> We have had the opportunity of studying the clinical and pathologic findings in four cases of a hitherto undescribed form of endocarditis, which we have for the present described as an atypical form of verrucous endocarditis. . . .
>
> The disease . . . ran a subacute course, with fever and progressive anemia. Briefly enumerated, the clinical findings were pericarditis, white-centered petechiae, arthritis, erythematous and purpuric rashes, ulcerative lesions of the mucous membranes, pleuropulmonary symptoms, embolic phenomena, enlargement of the liver and spleen, acute glomerulonephritis, a tendency to leukopenia and repeatedly negative blood cultures. Two of the patients had an eruption on the face which resembled acute lupus erythematosus disseminatus. . . .

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

WAGNER-MURRAY-DINGELL BILL

The following open letter was forwarded, as of December 2, to all Massachusetts members of the Senate and House of Representatives in Washington. It is expressive of the collective viewpoint of the medical societies of Maine, New Hampshire, Vermont, Massachusetts, Rhode Island and Connecticut regarding Senate Bill 1161 and House Bill 2861 — the so-called "Wagner-Murray-Dingell Bill."

Michael A. Tighe, *Secretary pro tempore*
New England Conference
Wagner-Murray-Dingell Bill

Massachusetts Medical Society
8 Fenway, Boston

December 2, 1943

Dear Sir:

The Massachusetts Medical Society, in conjunction with the medical societies of Maine, New Hampshire, Vermont, Rhode Island and Connecticut, has studied Senate Bill 1161 and House Bill 2861 now before the Congress of the United States and respectfully submits its views on this proposed legislation.

We approve of the broad medical objective of the act that we interpret to be an attempt to improve the health of the people. As a basis of our approval we cite the progressive leadership which the physicians of New England have always shown in the development of public-health enterprises. For more than fifty years we have consistently supported the plea for the establishment of a National Department of Health with a secretary in the President's Cabinet, under whom would be co-ordinated many important public-health programs, exclusive of the Army and Navy. These are now scattered through various departments and bureaus of the federal government and already play a large role in the provision of medical care for the people of this country.

We approve of the use of the insurance principle on a voluntary basis as a means to aid the individual to budget against the cost of medical care. We maintain that when insurance programs are not directly under the supervision of the medical profession by whom medical care is to be rendered, they should provide for cash benefits to be paid to the individual, for we firmly believe that the citizens of New England are capable of using cash benefits to pay the costs of medical care.

We believe that S. B. 1161 and H. B. 2861 do not provide for the sound development of a national health program. It is implied by the act that the distribution of compulsory savings managed by federal authorities will guarantee better health for all the people. We sincerely doubt that such an objective can be realized in this way. In the New England states, judged by any standards with which we are familiar, there is no need to revolutionize the habits of the people in their methods of obtaining medical care.

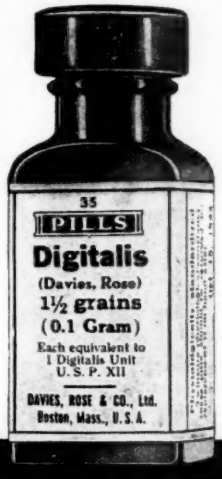
Private enterprises in the field of voluntary prepaid medical and hospital insurance are increasing rapidly. *These facilities should be utilized by the states, if necessary through federal grants-in-aid, so that each state can purchase medical care for those who cannot purchase it for themselves.* This we believe to be a development that would be acceptable to the New England people, for thereby medical care could be provided even for the indigent who are public charges, a provision most desirable in those communities that have been unable or unwilling to meet this obvious responsibility.

We shall be glad to work out plans with representatives of the federal and state governments to improve the health of all the people, but we should expect that any plans that might be devised would take full advantage of existing agencies and be developed within the social patterns that are well understood by our people.

Very truly yours,

[Signed] Roger I. Lee
Roger I. Lee, M.D., *President*
[Signed] Michael A. Tighe
Michael A. Tighe, M.D., *Secretary*

(Notices on page xiv)



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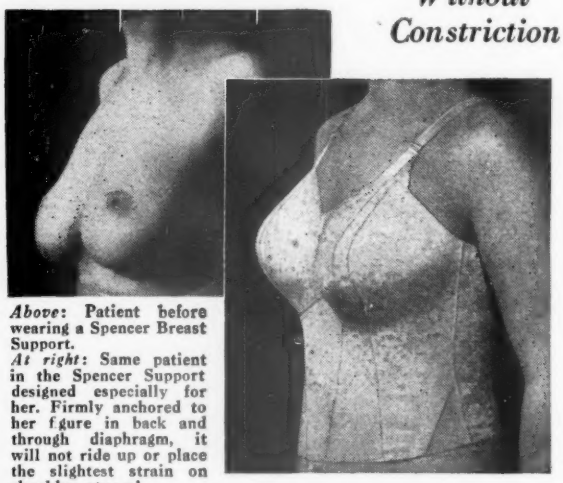

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NOTICES

BOSTON SOCIETY OF BIOLOGISTS

A meeting of the Boston Society of Biologists will be held in the Surgical Amphitheater of the White Building, Massachusetts General Hospital, on Wednesday, December 15, at 8 p.m.

PROGRAM

Histochemical Evidence of Thyroid Function. Dr. Edward W. Dempsey.

On the Action of Goitrogenic Agents. Dr. J. H. Means.

Clinical and Pharmacological Properties of Thiouracil. Dr. Robert H. Williams.

Dinner will be served in the Pay Cafeteria in the East Dining Room of the White Building at 6:30 p.m. (price, 60 cents).

AMERICAN BOARD OF OPHTHALMOLOGY

The American Board of Ophthalmology announces the following examinations: New York City, June, deadline, December 15, 1943; Chicago, October, deadline, April 1, 1944.

All applications received after January 1, 1944, will be subject to the increased total fee of $75.00.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston
Lecture Hall, 9–10 a.m.

MEDICAL CONFERENCE PROGRAM

Friday, December 3 — Some Studies in the Socio-Economic Relationships of Disease. Major Robert Hyde.

Wednesday, December 8 — Clinical Significance of Serum Phosphatase. Dr. Martin Nothmann.

Friday, December 10 — Studies in Human Fertility (motion picture film). Ortho Products, Inc.

Wednesday, December 15 — Insulin and Insulin Mixtures. Dr. Joseph Rosenthal.

Friday, December 17 — Certain Atypical Forms of Rheumatoid Arthritis. Dr. Marian Ropes.

On Tuesday and Thursday mornings Dr. S. J. Thannhauser will give medical clinics on hospital cases.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, DECEMBER 9

THURSDAY, DECEMBER 9

*9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

5:00 p.m. Some Neurosurgical Problems in Early Life. Dr. Francis Ingraham. Children's Hospital, Boston.

FRIDAY, DECEMBER 10

*9:00–10:00 a.m. Studies in Human Fertility (motion picture film) Ortho Products, Inc. Joseph H. Pratt Diagnostic Hospital.

SATURDAY, DECEMBER 11

*10:00–11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

MONDAY, DECEMBER 13

*12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

TUESDAY, DECEMBER 14

*9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

2:00–4:00 p.m. Myasthenia gravis clinic. Out Patient Department. Massachusetts General Hospital.

(Notices continued on page xvii)

WEDNESDAY, DECEMBER 15
*9:00-10:00 a.m. Insulin and Insulin Mixtures. Dr. Joseph Rosenthal. Joseph H. Pratt Diagnostic Hospital.
*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.

DECEMBER 3–17. Joseph H. Pratt Diagnostic Hospital. Medical conference program. Page xiv.

DECEMBER 15. Boston Society of Biologists. Page xiv.

JANUARY 13. Sudden Death. Dr. Alan R. Moritz. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

FEBRUARY 12. American Board of Obstetrics and Gynecology. Page ix, issue of October 28.

MAY 23 and 24. Massachusetts Medical Society. Annual meeting, Hotel Statler, Boston.

JUNE 12–16. American Medical Association. Annual meeting. Chicago. Page 798, issue of November 18.

DISTRICT MEDICAL SOCIETY

WORCESTER
DECEMBER 8. Worcester City Hospital.
JANUARY 12. Memorial Hospital, Worcester.
FEBRUARY 9. Worcester State Hospital, Worcester.
MARCH 8. St. Vincent Hospital, Worcester.
APRIL 12. Hahnemann Hospital, Worcester.
MAY 10. Annual meeting.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Whooping Cough. By Joseph H. Lapin, M.D., adjunct pediatrician, Bronx Hospital, and associate in contagion, Riverside Hospital for Contagious Diseases, New York City. 8°, cloth, 238 pp., with 25 tables. Springfield, Illinois: Charles C Thomas, 1943. $4.50.

This monograph covers all the important phases of whooping cough, and the author has tried to present an adequate digest of the covering literature. In addition, his own experiences in clinics and in a contagious-disease hospital have been incorporated in their proper places in the text.

The National Malnutrition. By D. T. Quigley, M.D. 8°, cloth, 113 pp. Milwaukee, Wisconsin: The Lee Foundation for Nutritional Research, 1943. $1.00.

The author believes that there is a badly diseased population in the United States owing to deficiency diets. He outlines the program of what should be done to remedy this situation. He discusses the dietary needs of the ordinary person and the importance of vitamins and minerals in the normal diet.

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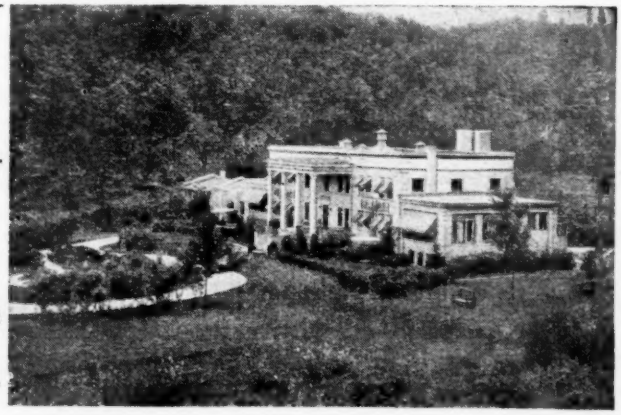

The rooster's legs are straight.

The boy's are not.

The rooster got plenty of vitamin D.

Fortunately, extreme cases of rickets such as the one above illustrated are comparatively rare nowadays, due to the widespread prophylactic use of vitamin D recommended by the medical profession.

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